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AND
PROCESSES OF
AGING

VOLUME 16 NUMBER 8
AUGUST 1961

Geriatrics

Special Issue on
Cardiovascular Diseases

63-12856

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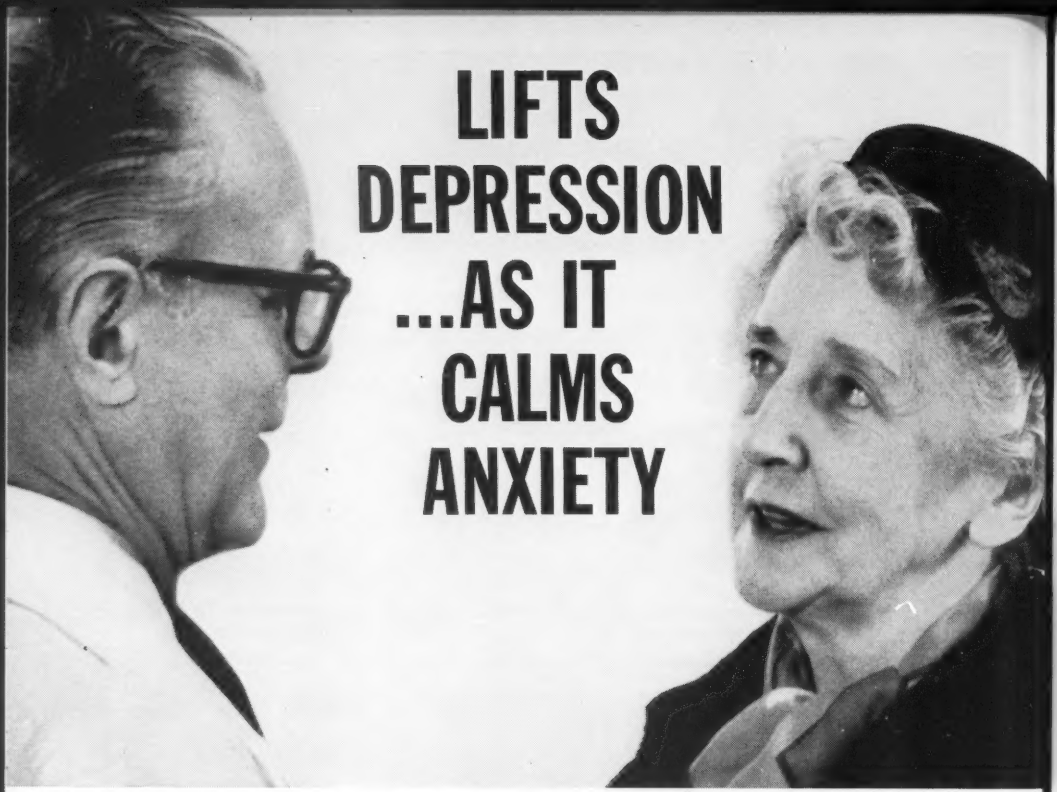

"I feel much better, thank you." Your balanced Deprol therapy has lifted her depression and brightened up her mood—while her anxiety and tension have been calmed down. She sleeps better, eats properly, and normal drive and interest have replaced her emotional fatigue.

Brightens up the mood, brings down tension

Deprol's balanced action avoids "seesaw" effects of energizers and amphetamines. While energizers and amphetamines may stimulate the patient – *they often aggravate anxiety and tension.*

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These "seesaw" effects are avoided with Deprol. It lifts depression as it calms anxiety – a balanced action that brightens up the mood, brings down tension, and relieves insomnia, anorexia and emotional fatigue.

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Acts safely – no danger of liver or blood damage. Deprol does not cause liver toxicity, anemia, hypotension or psychotic reactions – frequently reported with other drugs.

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▲Deprol▲®

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Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

CD-4490

Established 1946

Volume 16
Number 8

Geriatrics

AUGUST 1961

Special Issue

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Patient M. J. ... one of the growing thousands of hypertensive patients controlled by Ismelin®

Mr. M.J., now 61, was admitted to a large teaching hospital in 1957 with mild pulmonary edema and severe hypertension (300/170 mm. Hg). Digitalis was given, along with reserpine and a ganglionic blocker.* He was discharged 16 days later, with blood pressure of 130/70 mm. Hg standing and 170/110 supine. Blood pressure, within 4 weeks, was 170/105 mm. Hg (sitting and standing). But ganglion-blocker therapy (alone or combined with chlorothiazide and/or rauwolfia) failed to hold blood pressure down and the side effects —syncope, lightheadedness, difficulty in evacuation and micturition— became increasingly troublesome.

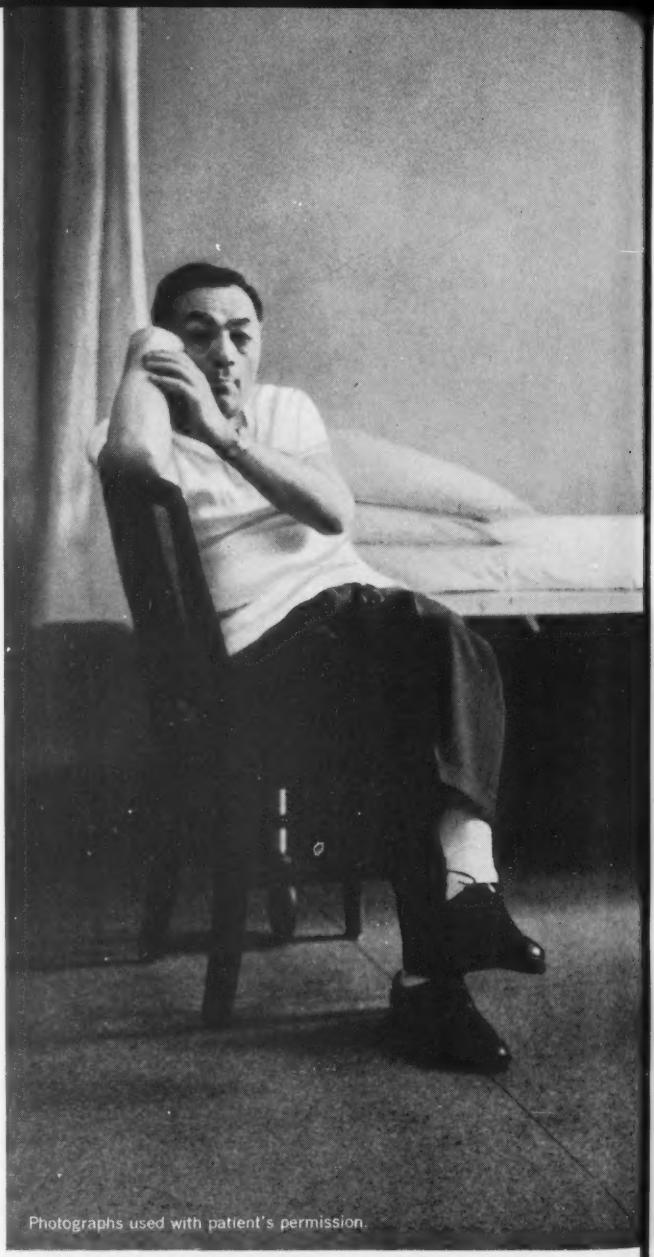
Blood pressure controlled with Ismelin— patient active and comfortable

On March 1, 1960, the ganglionic blocker was replaced with SU-5864 (Ismelin†). Within 5 weeks, Mr. J. was nearly normotensive and "felt 100% better."

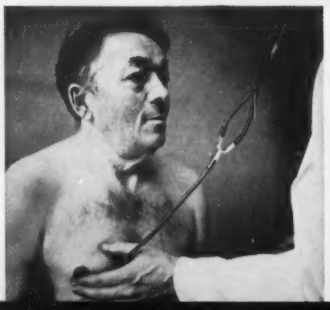
As of October 5, 1960, blood pressure was 174/100 sitting and 130/80 standing. There was no evidence of tolerance to Ismelin.

*Therapy for this patient, during the 3½ years of treatment described here, included digitalis and one or more of the following: rauwolfia, thiazides, Serpasil-Apresoline.
†SU-5864 was introduced by CIBA as Ismelin® on July 5, 1960.

CIBA
SUMMIT•NEW JERSEY



Photographs used with patient's permission.



..."the most important new drug for the treatment of hypertension..."[1]

Following are representative comments from the ever-increasing published reports on Ismelin:

Patients on Ismelin have controlled blood pressures

"Only 1 of the 27 patients did not respond to treatment....The reduction of the systolic and diastolic pressures averaged 11/13 per cent in the supine position, 17/17 per cent in the sitting position, and 25/22 in the erect position. There were, of course, varying responses in the blood pressure from patient to patient, but generally blood pressure reduction was consistent in all three positions. The postural effect was most striking."[2]

"...Guanethidine [Ismelin] is a potent agent which lowers the diastolic pressure in many cases previously resistant to therapy with rauwolfia, hydralazine, hydrochlorothiazide, and ganglionic blockade."[3]

"Though our experience is limited, we have little doubt that guanethidine [Ismelin] is at present the drug of choice [for severe hypertension]. Its action is apparently steady; tolerance does not develop; and outpatient care of cases is relatively easy."[4]

"The use of this extremely potent drug led in all cases, which were treated both in hospital and on an ambulatory basis, to a clear-cut reduction in blood pressure, often even to normal levels."[5]

Hypertensive patients on Ismelin are relatively comfortable

Ismelin, because it is the selective sympathetic inhibitor, allows patients to be relatively comfortable. Ismelin suppresses sympathetic function with virtually no effect on the parasympathetic nervous system.

"In contrast [to the ganglionic blocking agents], guanethidine [Ismelin] is a purely sympatholytic agent with a hypotensive potency similar to that of the ganglion blocking compounds but with a lesser incidence of accompanying untoward effects."[6]

"The absence of tachycardia distinguishes the action of guanethidine [Ismelin] from that of adrenergic blocking drugs..."[2]

"Guanethidine [Ismelin], administered alone, was given to 40 hypertensive patients without serious side effects."[7]

"Notably absent were the constipation, paresis of visual accommodation, and dry mouth characteristic of the parasympatholytic effects of ganglion blocking drugs."[8]

"The absence of constipation was especially noteworthy."[9]

"Diarrhea has been mild and easily controlled."[10]

"Dry mouth, constipation, and difficulty in micturition were not encountered in this study. Those patients who had previously been on ganglion blocking therapy were relieved of these symptoms remarkably quickly, as well as of blurring of vision, when [Ismelin] was substituted."[11]

"No serious side effects were seen, and all could be alleviated or abolished by reducing the dosage."[7]

Physicians note that patients prefer Ismelin

"The majority of patients preferred guanethidine [Ismelin] over their previous antihypertensive medications; those previously treated with ganglionic blocking agents were particularly grateful for relief of constipation and visual difficulties."[7]

"We believe that use of it lessened anxiety in our patients. Most were better satisfied with guanethidine than they had been with previous ganglion blocker therapy."[11]

"Unlike the impotence experienced after ganglionic blocking agents, ability to obtain an erection was not impaired."[2]

"Guanethidine [Ismelin] has remarkably few side effects. The absence of symptoms of parasympathetic blockade makes its use better tolerated by most patients than conventional ganglion blocking therapy."[11]

"Most patients who had been treated previously with ganglion-blocking drugs expressed a strong preference for guanethidine."[12]

"Life need no longer be made a misery by the parasympathetic effects of the ganglion-blocking agents."[4]

For complete information about Ismelin (including dosage, cautions, and side effects), see 1961 Physicians' Desk Reference or write CIBA, Summit, N. J.

SUPPLIED: Tablets, 10 mg. (pale yellow, scored) and 25 mg. (white, scored); bottles of 100.

REFERENCES: 1. Kirkendall, W. M., Freis, E. D., and Moyer, J. H.: Summary of panel discussion, "New Drugs in the Treatment of Hypertension," presented at the 33rd Scientific Sessions of the American Heart Association, St. Louis, Mo., Oct. 21, 1960. **2.** Frohlich, E. D., and Freis, E. D.: Paper presented at a Symposium on Guanethidine (Ismelin®), The University of Tennessee College of Medicine, Memphis, Tenn., April 22, 1960. **3.** Clark, G. M., Edmonson, J., and Lefkovits, A.: Ibid. **4.** Evanson, J. M., and Sears, H. T. N.: Lancet 2:387 (Aug. 20) 1960. **5.** Jaquerod, R., and Spühler, O.: Schweiz. med. Wchnschr. 90:113 (Jan. 30) 1960 (translation). **6.** Brest, A. N., and Moyer, J. H.: Paper presented at a Symposium of Guanethidine (Ismelin®), The University of Tennessee College of Medicine, Memphis, Tenn., April 22, 1960. **7.** Eagan, J. T., and Orgain, E. S.: Ibid. **8.** Richardson, D. W., and Wyso, E. M.: Virginia M. Month. 86:377 (July) 1959. **9.** Ford, R. V., and Fallis, N.: Paper presented at a Symposium on Guanethidine (Ismelin®), The University of Tennessee College of Medicine, Memphis, Tenn., April 22, 1960. **10.** Page, I. H., and Dustan, H. P.: J.A.M.A. 170:1265 (July 11) 1959. **11.** Kirkendall, W. M., Fitz, A. M., Van Hecke, D. C., Wilson, W. R., and Armstrong, M. L.: Ibid. **12.** Dollery, C. T., Emslie-Smith, D., and Milne, M. D.: Lancet 2:381 (Aug. 20) 1960.

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ESIDRIX® (hydrochlorothiazide CIBA)

Ismelin®

sulfate
(guanethidine sulfate CIBA)

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INFORMATION FOR AUTHORS

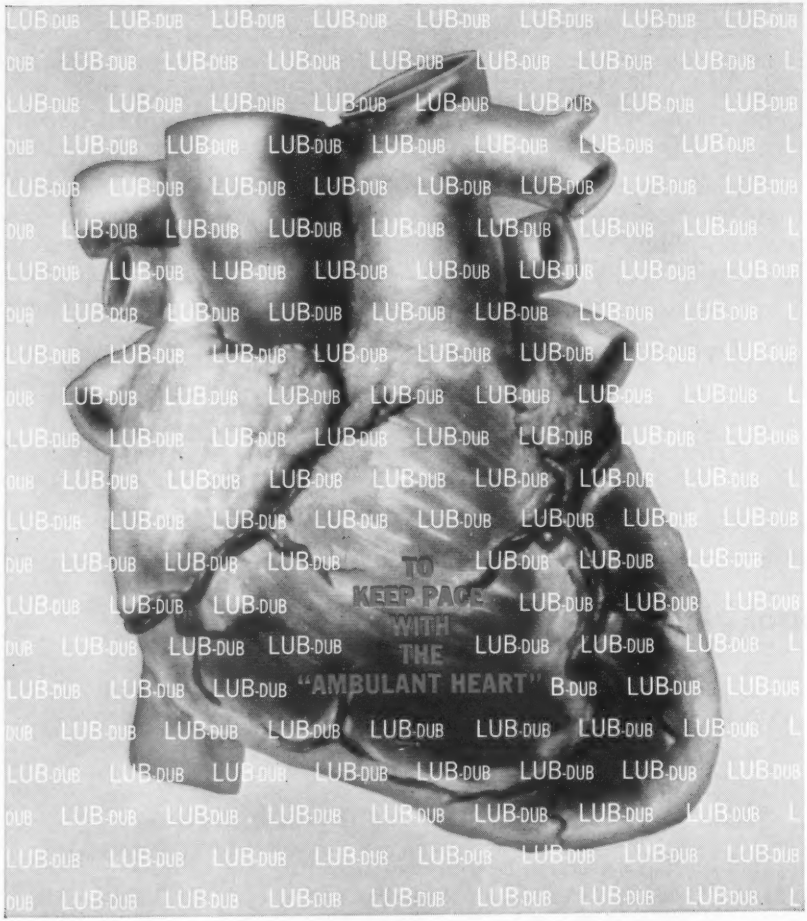
The editors of GERIATRICS invite physicians to submit original papers in the field of geriatric medicine. Interest and value to the practicing physician are paramount.

Manuscripts should be typewritten, double spaced. Recommended length is from 3,500 to 5,000 words. Authors' full names, academic or professional affiliation, and complete addresses should be included. No more than three names should be listed. Credit to contributing workers may be given in a footnote.

Titles should consist of 4 to 6 words. References should be kept to not more than 20 citations and should be typed on a separate sheet. Both journal and book references should follow the style of the *Index Medicus*. References are to be numbered and listed consecutively as they appear in the manuscript. A summary of 40 to 60 words for use at the head of the article should accompany the manuscript.

GERIATRICS encourages the use of illustrations. Art work and photographs must be clear, sharp, and suitable for good reproduction. Each illustration should be fully identified with author's name and with figure number and should be accompanied by cutlines numbered to correspond. Tables must be well organized, clear, and accurate, and each should be typed on a separate sheet.

Galley proofs and reprint order cards will be submitted to the senior author well in advance of publication date. Manuscripts should be directed to the Editorial Department, GERIATRICS, 84 South Tenth Street, Minneapolis 3, Minnesota.



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Bibliography:

1. Ernst, E. M.: *Pennsylvania M.J. 63*:708 (May) 1960.
2. Settel, E.: *Clin. Med. 7*:1835 (Sept.) 1960.

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after 3 years' clinical experience:
here is what we now know about MER/29 and

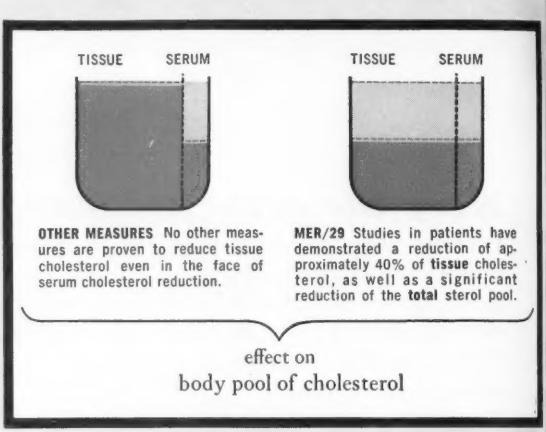
WE KNOW HOW MER/29 ACTS

We know that MER/29 lowers cholesterol in 8 out of 10 patients, even without dietary restrictions. In 576 patients studied by various physicians, average cholesterol levels dropped from 303 mg. % to 241 mg. % — an average decrease of 62 mg. %.

We know that MER/29 reduces total sterols in both blood and tissue.

We know that MER/29 does this by inhibiting the body's own production of cholesterol.

We know that its use in over 300,000 patients re-affirms the safety margins established in early laboratory and clinical data.


TISSUE
SERUM
TISSUE
SERUM
OTHER MEASURES No other measures are proven to reduce tissue cholesterol even in the face of serum cholesterol reduction.
MER/29 Studies in patients have demonstrated a reduction of approximately 40% of tissue cholesterol, as well as a significant reduction of the total sterol pool.
effect on
body pool of cholesterol

WE KNOW THE BENEFITS OF MER/29

We know that, in some patients, concurrent clinical benefits attend the use of MER/29. Published papers on MER/29 therapy to date report improvement in 50 of the 79 anginal patients reported in these studies, and comparable results are being obtained in similar studies now in progress. Among the other benefits reported are:

decreased incidence and severity of anginal attacks
improved ECG patterns
diminished nitroglycerin dependence
increased sense of well-being

"During triparanol [MER/29] therapy there was a definite improvement in the electrocardiographic tracings in response to exercise in 3 of 11 subjects with angina pectoris."
—*Hollander, W.,* et al.: *J.A.M.A.* 174:*5 (Sept. 3) 1960.*

"Nitroglycerin requirements decreased in 3 [of 5 out-patient] patients, including the patient showing electrocardiographic improvement....Three [of 4 private male patients], after a lapse of some weeks, showed improvement in exercise electrocardiograms, which was sustained but not further improved in subsequent observations."
—*Corcoran, A. C.,* et al.: *Progr. Cardiovasc. Dis.* 2:*(Pt. 1) 576 (May) 1960.*

"Of the 45 patients with coronary artery disease followed for 1 year, 16 had a history of frequent anginal attacks. Fourteen of these spontaneously stated that their angina disappeared within 2 months of [MER/29] therapy....In one patient...with persistent coronary insufficiency pattern (ST segment depressions in multiple leads), there was a complete reversion to a normal tracing during MER/29 therapy with associated clinical improvement in angina."
—*Lisan, P.: Progr. Cardiovasc. Dis.* 2:*(Pt. 1) 618 (May) 1960.*

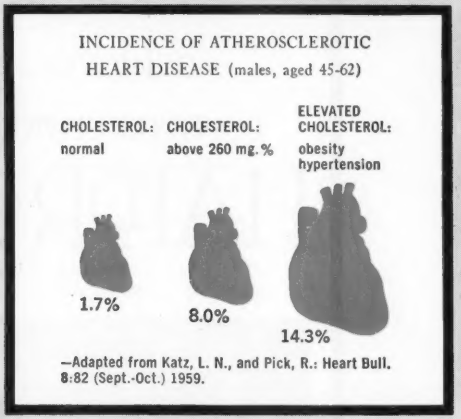
. . . what we are learning about atherosclerosis

WHY MER/29 MAY FAVORABLY ALTER ATHEROSCLEROSIS

"It has become generally accepted that elevated blood cholesterol or lipid, if sustained long enough, leads to early atherosclerosis."
–Page, I. H.: Mod. Med. 29:71 (Mar. 20) 1961.

Epidemiologic studies show that low cholesterol levels are associated with low incidence of atherosclerosis and coronary artery disease.

On the basis of such studies, Stamler has said: "...a 15 to 20 per cent reduction in mean serum cholesterol levels alone might be associated with a 25 to 50 per cent reduction in coronary disease incidence rates in middle-aged men."
–Stamler, J.: Am. J. Pub. Health 50:(Pt. 2) 14 (Mar.) 1960.


INCIDENCE OF ATHEROSCLEROTIC HEART DISEASE (males, aged 45-62)
CHOLESTEROL: normal
CHOLESTEROL: above 260 mg.%
ELEVATED CHOLESTEROL: obesity hypertension
1.7%
8.0%
14.3%
–Adapted from Katz, L. N., and Pick, R.: Heart Bull. 8:82 (Sept.-Oct.) 1959.

THE DECISION FACING THE PHYSICIAN

Despite our knowledge of the action, benefits and safety of MER/29, much remains to be discovered about the basic concept of cholesterol-lowering therapy. In this, MER/29 is comparable to the well-accepted use of antihypertensive agents: we know they lower blood pressure, but we cannot prove that lowering blood pressure will also lower morbidity or mortality. Yet few physicians hesitate to use these agents. The possible good is too great to ignore.

So it is with MER/29. No one can yet be certain that sustained lowering of total body sterols will prevent or alter atherosclerosis. But the current evidence strongly supports this concept.

Perhaps that is why an increasing number of physicians are now prescribing MER/29. They wish to assure their hypercholesterolemic, coronary artery disease, and atherosclerotic patients this reasonable hope.

It is a decision facing every physician.

Complete bibliography and prescription information on request.

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	Triamcinolone or methylprednisolone	4 mg.
	Dexamethasone	0.75 mg.

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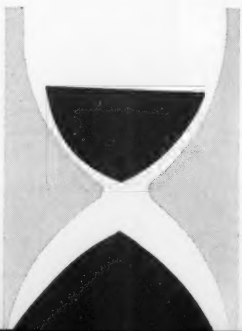


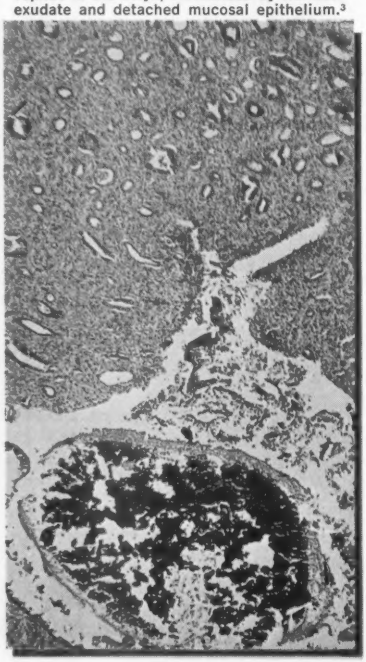
Geriatrics

GOUT

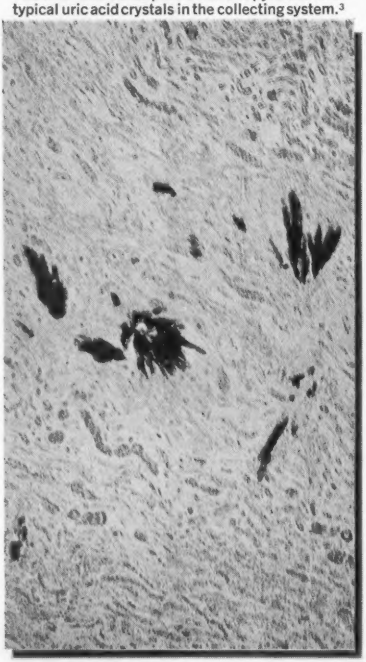
"For centuries the victims of gout have been the subject of lampoons and caricatures. We now know that they should rather be the objects of great concern, for the disease is painful, disabling and is accompanied by complications that impair health and shorten life."[1]

Kidney impairment, with varying degrees of hypertension and arteriosclerosis, is the critical complication of gout. "From 30 to 50 per cent of gouty patients are said to die of renal disease."[2]

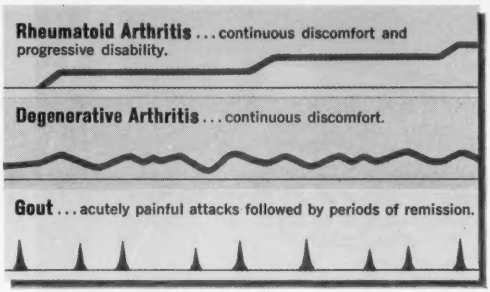
Tophus in the calyx, surrounded by fibrinoid exudate and detached mucosal epithelium.[3]

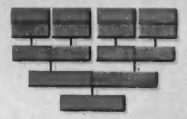


The mid- and outer portion of the pyramid with typical uric acid crystals in the collecting system.[3]



AIDS TO DIAGNOSIS


Rheumatoid Arthritis ... continuous discomfort and progressive disability.
Degenerative Arthritis ... continuous discomfort.
Gout ... acutely painful attacks followed by periods of remission.



"If a family history of gout is obtained, even though it is one or two generations removed, this information is significant."[4]

"The metatarsophalangeal joint of a great toe is affected early or repeatedly in some cases, rarely or never in others."[6]

"All patients complaining of non-traumatic musculoskeletal discomfort should have at least one serum uric acid determination."[5]

Colchicine test: "Colchicine should be administered as early as possible after the onset of articular distress, 1 mg.... every 2 hours until the onset of gastro-intestinal distress. From 5 to 8 mg. usually are required."[9] Pain relief is highly indicative of gout.

THE "INSULIN OF GOUT"[7]

"Of the various drugs with uricosuric activity, probenecid [BENEMID] has proved most desirable for long-term administration."[8]

BENEMID®

PROBENECID

Therapy with BENEMID should be continued without interruption since hyperuricemia recurs when dosage is terminated. The rare patient who experiences gastric discomfort is usually benefited by decreasing the dosage. Dosage: 0.25 Gm. twice daily for one week, followed by 1 Gm. daily in divided doses. Supply: 0.5 Gm. tablets.

A COMPLEMENTARY FORMULATION OF TWO CLASSIC ANTI-GOUT AGENTS

"... the greater the experience we have with the combination of colchicine and Benemid the greater the reliance we place upon these two drugs."[9]

ColBENEMID®

COLCHICINE WITH BENEMID

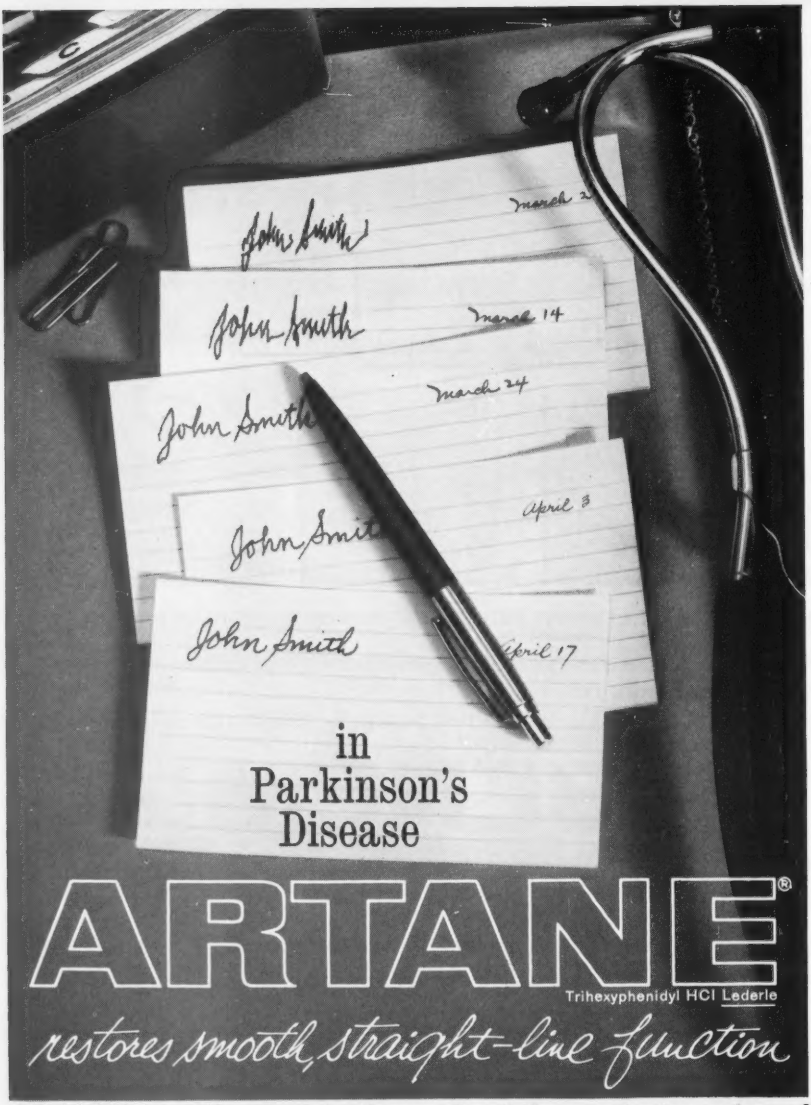
Dosage: One tablet daily for one week, followed by one tablet twice daily. Supply: Each tablet contains 0.5 mg. colchicine and 0.5 Gm. BENEMID. Bottles of 100 and 1000.

1. Cornish, A. L.: J. Kentucky M.A. 58:707, June, 1960. 2. Wyngaarden, J. B.: Arthritis & Rheumatism 1:191, June, 1958. 3. Talbott, J. H. and Terplan, K. L.: Medicine 39:405, Dec., 1960. 4. Talbott, J. H.: Gout, New York, Grune & Stratton, 1957, p. 123. 5. Kuzell, W. C., et al.: J. Chron. Dis. 2:645, Nov., 1955. 6. Hench, P. S.: Gout and gouty arthritis, in Cecil, R. L.: A textbook of medicine, ed. 10, Phila., W. B. Saunders Co., 1959. 7. Bartels, E. C., and Kepkay, P. H.: Bull. Vancouver M.A. 29:306, April, 1953. 8. Boland, E. W.: World-Wide Abstracts of Gen. Med. 3:16, Jan., 1960. 9. Talbott, J. H.: Current Med. Dig. 26:57, Nov., 1959.

Before prescribing or administering BENEMID or ColBENEMID, the physician should consult the detailed information on use accompanying the package or available on request.

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

BENEMID AND COLBENEMID ARE TRADEMARKS OF MERCK AND CO., INC.



ARTANE is well suited to the needs of the greatest number of patients.[2] Improves rigidity, akinesia and mental depression. Controls oculogyria . . . remarkably free of toxic reactions.[1]

Indicated: All types of Parkinsonism, and to control extrapyramidal reactions in ataractic therapy. Supplied: Tablets, 2 mg. and 5 mg.; Elixir, 2 mg./5 cc. tsp. 1. Constable, K.: J. Am. M. Women's A. 15:757 (Aug.) 1960. 2. Critchley, M.: Brit. M. J. 2:1214 (Nov. 15) 1958.

Request complete information on indications, dosage, precautions and contraindications from your Lederle Representative or write to Medical Advisory Department.

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

Clinically Proven

in more than 750 published clinical studies
and over six years of clinical use

Outstandingly Safe and Effective

for the tense and nervous patient

1. simple dosage schedule relieves anxiety dependably – without the unknown dangers of "new and different" drugs
2. does not produce ataxia, stimulate the appetite or alter sexual function
3. no cumulative effects in long-term therapy
4. does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis
5. does not muddle the mind or affect normal behavior

Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; bottles of 50. Also as MEPROTABS*–400 mg. *unmarked*, coated tablets; and in *sustained-release* capsules as MEPROSPAN®-400 and MEPROSPAN®-200 (containing respectively 400 mg. and 200 mg. meprobamate).
*TRADE-MARK

Miltown®

meprobamate (Wallace)

WALLACE LABORATORIES / *Cranbury, N. J.*

CM-4731

Help protect the precarious

Older patients often need help when they complain of dizziness . . . help that can be provided by Dramamine. This classic drug is free of serious side effects, easy-to-take and frequently is effective against dizziness with a vestibular component whether acute or chronic. These elder citizens will be grateful for Dramamine.

Dramamine®
brand of dimenhydrinate
for dizziness/vertigo in older patients

Dosage: one 50-mg. tablet, t.i.d.

Research in the Service of Medicine SEARLE

TO FUTURE ISSUES

▶ *The Thyroid Gland After Age 50.* Involution of the thyroid gland after the age of 50 appears to be a physiologic reaction to diminished requirements of the organism for thyroxin, according to R. P. Stoffer and associates of the Hertzler Clinic and Hertzler Research Foundation, Halstead, Kansas. Histologic examination of 141 thyroid glands from individuals over 50 showed evidence of enough functional units to satisfy the decreased demand for thyroid hormones. At the same time, functional studies on 282 old euthyroid individuals showed a lower rate of radioiodine accumulation by thyroid but a normal amount of protein bound iodine in the serum. The discrepancy between the two tests can be explained by a decrease in utilization of thyroxin by the peripheral tissues.

▶ *Effect of Intravenous Heparin on Alimentary Lipemia.* In an effort to determine the effect of heparin on alimentary lipemia, M. Toor and associates of the Beilinson Hospital in Petah Tiqvah, Israel, conducted studies on three different groups of patients —(1) 15 healthy, recently immigrated Yemenites, (2) 25 healthy subjects of European origin, and (3) 18 men of European origin, who had had myocardial infarction twice. There was no significant difference in heparin-induced postprandial clearing or in the heparin-induced shift of alpha and beta lipoproteins among the three groups.

▶ *Aging in the Connective Tissues of the Human Musculoskeletal System.* Because of the scarcity of published material on the connective tissues of the human musculoskeletal system, Edgar M. Bick of the Orthopedic Service and Orthopedic Research Laboratory, Mount Sinai Hospital, New York City, conducted two laboratory studies on such tissue from living human beings—the first on the fascia lata, the specimens of the second study stained to emphasize the elastic fibers. These studies showed that the connective tissues are remarkably stable with advancing age. Degeneration of elastic fibers, which occurs in isolated areas, may be caused by normal metabolic changes or may represent the scars of multiple traumata of a long life.

▶ *Farm Retirement in the United States.* Voluntary retirement of farmers is a relatively recent phenomenon in the United States, says Lowry Nelson, professor emeritus of sociology, University of Minnesota. Even among commercial farmers, retirement is faced with great reluctance. Many remain active until death, although they work at a slower pace. Most of those who do retire prefer to continue living on the farm, but some move to towns and cities. They prefer to live by themselves rather than with their children. As coverage of OASI increases, more farmers may choose to retire earlier than they ordinarily would.

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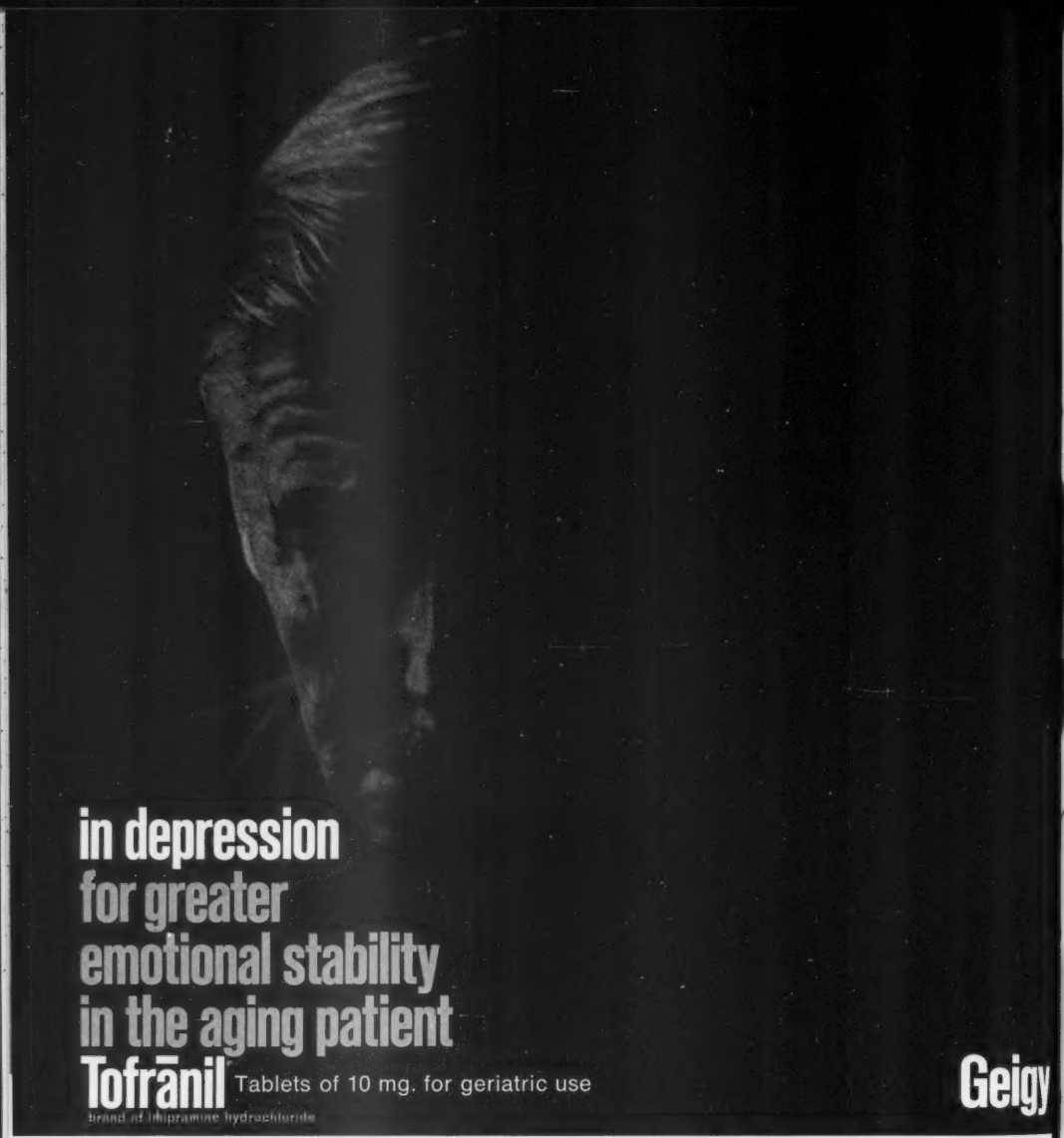
ADVERTISING REPRESENTATIVES, NEW YORK 17: Burt D. Cohen, Ron Ziegler, Bernard A. Smiler, John Winter, George B. Janco, 1 East 42nd Street. Telephone: Murray Hill 2-8717.

CHICAGO 6: Greg Gelderman, Jay H. Herz, Hugh Gibson, 20 North Wacker Drive. Telephone: Central 6-4619.

SAN FRANCISCO 4: Duncan A. Scott & Co., Fifth Floor, 85 Post Street. Telephone: Garfield 1-7950.

LOS ANGELES 57: Duncan A. Scott & Co., 1901 West 8th Street. Telephone: Hubbard 3-6211.



in depression for greater emotional stability in the aging patient

Tofrānil Tablets of 10 mg. for geriatric use

Brand of imipramine hydrochloride

Geigy

During the declining years, frustration arising from declining capacity to participate in social and family activities often leads to depression, manifested frequently in unpredictable swings of mood.[1]

The value of Tofrānil in restoring the depressed elderly patient to a more normal frame of mind has received strong support from recent studies.[1-3] Under the influence of Tofrānil, such symptoms as irascibility, hostility, apathy and compulsive weeping are often strikingly relieved with the result that life becomes easier both for the patient and those around him.

Since the dosage requirements of elderly patients are lower than those of the non-geriatric patient, Tofrānil is made available in a special low dosage 10 mg. tablet designed specifically for geriatric use.

Full product information regarding dosage, side effects, precautions and contraindications available on request.

References: 1. Cameron, E.: Canad. Psychiat. A. J., Special Supplement **4**:S160, 1959. 2. Christe, P.: Schweiz. med. Wchnschr. **90**:586, 1960. 3. Schmied, J., and Ziegler, A.: Praxis **49**:472, 1960.

Tofrānil®, brand of imipramine hydrochloride: Triangular tablets of 10 mg. for geriatric use; also available, round tablets of 25 mg., and ampuls for intramuscular administration only, each containing 25 mg. in 2 cc. of solution (1.25 per cent).

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York

TO-657-6

Hypertension of 7 years' duration yields to Ser-Ap-Es®

Photo used with patient's permission.

Combination brings blood pressure down after other agents fail—During the past 7 years, Mrs. E. A.'s hypertension gradually advanced in severity. In 1956 and 1957 multiple retinal hemorrhages occurred in the right eye, and vision in this eye deteriorated. Retinopathy advanced to Grade III; EKG showed left ventricular hypertrophy; renal studies showed increasing involvement.

A wide variety of antihypertensive agents (including ganglionic blockers) failed to stabilize blood pressure at satisfactory levels or caused troublesome side effects.

When therapy with Ser-Ap-Es was started, Mrs. A.'s blood pressure (sitting and standing) was 230/120 mm. Hg. With Ser-Ap-Es, blood pressure (sitting and standing) has now been reduced to 190/90, and Mrs. E. A. enjoys a measure of control that had not been achieved with previous agents.

Because it provides 4 actions—central, cardiac, renal, and vascular—in one convenient tablet, Ser-Ap-Es can help you bring more of your hypertensive patients under control.

SUPPLIED: *Tablets* (salmon pink), each containing 0.1 mg. Serpasil, 25 mg. Apresoline hydrochloride, and 15 mg. Esidrix.

For complete information about Ser-Ap-Es (including dosage, cautions, and side effects), see Physicians' Desk Reference or write CIBA, Summit, N. J. 2/3923MK

SERPASIL® (reserpine CIBA)
APRESOLINE® hydrochloride (hydralazine hydrochloride CIBA)
ESIDRIX® (hydrochlorothiazide CIBA)

The actions of Serpasil®, Apresoline® and Esidrix® in a single tablet:

Ser-Ap-Es®

CIBA SUMMIT, NEW JERSEY

Inflammatory reaction following stress!

In inflammation, either localized or generalized in nature, capillary damage – increased permeability, resulting in seepage of blood constituents into the tissues – is a uniform basic reaction resulting from injury or stressors of various types:

PHYSICAL: Trauma, surgery, overexertion, sprains

NUTRITIONAL: Malnutrition, toxins, pregnancy, growth

ENVIRONMENTAL: Temperature, pressure, radiation, allergies

DISEASE STATES: Viral, bacterial, malignancies, endocrine

The role of the citrus bioflavonoids in the prevention or reversal of the inflammatory process is multiple through:

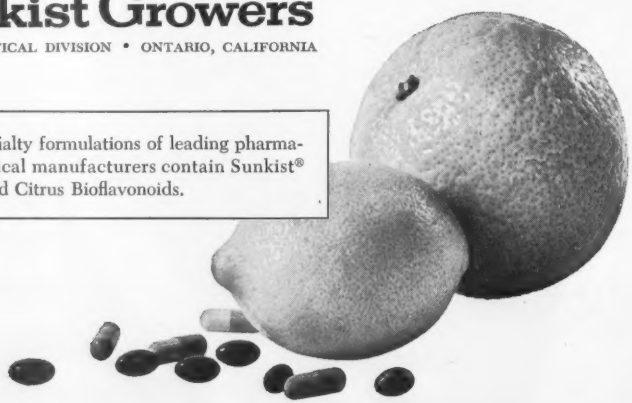
1. Maintenance of capillary integrity
2. In cellular metabolic processes, by potentiating corticosteroids, vitamins and essential nutrients, and by inhibition of hyaluronidase
3. Direct anti-inflammatory action

In the treatment of inflammatory conditions include the citrus bioflavonoids (Lemon Bioflavonoid Complex, Hesperidin Complex and Hesperidin Methyl Chalcone) as therapeutic adjuncts.

Sunkist Growers

PHARMACEUTICAL DIVISION • ONTARIO, CALIFORNIA

Specialty formulations of leading pharmaceutical manufacturers contain Sunkist® Brand Citrus Bioflavonoids.



new
anadrol™

reverses the wasting process-
provides solid weight gain

Dosage and administration—Adults: Anadrol is administered orally. The usual adult dosage is 2.5 mg. three times daily. The majority of patients show a favorable result at 7.5 mg./day. However, because of its comparatively low degree of androgenicity, doses up to 15 mg./day may be employed. Results have been seen in 10 days, but optimal results are usually obtained in 4 to 6 weeks. Therapy may have to be continued to sustain improvement according to the needs of the individual patient. **Children:** Adequate response has been observed in children up to the age of 12 years on dosage schedules of 2.5 mg./day and 5 mg./day. Children over 12 years of age may be given adult doses.
Precautions—Side effects with Anadrol have been minimal when administered in the recommended daily dosage range. In those few instances where masculinizing effects have been noted in adults or children, reversal has been accomplished after discontinuing therapy. Although Anadrol exhibits only a slight androgenicity, it shares with all androgens a tendency to favor sodium retention. For this reason, the drug should be used with caution in patients with heart disease. Administration to children should not be continued beyond a 30-day period because of increased sensitivity to masculinizing agents. If such masculinizing symptoms develop, this drug should be discontinued.
Contraindications—Anadrol is contraindicated in the presence of carcinoma of the prostate and, because of changes which have been observed in hepatic function on long-term use with Anadrol at higher doses, it should be used with caution in patients with known hepatic damage. It is also contraindicated in nephritis and nephrosis.
How supplied—Anadrol 2.5 mg. is supplied in bottles of 50 white, monogrammed tablets.

PRODUCT BROCHURE
ON REQUEST

anadrol
oxymetholone, Syntex

ANABOLIC
STEROID

reverses the wasting process—provides solid weight gain

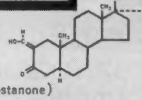
- **Anadrol stimulates nitrogen retention with 4 times the potency of methyltestosterone.***
- **Anadrol produces solid weight gain, not transient fluid retention.**
- **Anadrol is half as androgenic as methyltestosterone.***
- **Anadrol (oxymetholone) is lower in virilization.***
- **Anadrol, because of minimal side effects, is ideally suited for prolonged therapy.**
- **Anadrol is indicated for use in malnutrition and a wide range of catabolic disorders marked by a negative nitrogen balance.**

***As determined in man**

this preparation for use in:

Geriatric debilitation	Convalescence from infection
Chronic underweight	Gastrointestinal disease
Pre- and postoperative conditions	General catabolic conditions
Osteoporosis	Malnutrition

anadrol



(2-hydroxymethylene-17α-methyl-17β-hydroxy-3-androstanone)

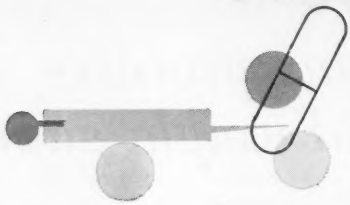
an original steroid from Syntex

SYNTEX

61 SU-1

Geriatrics

THERAPEUTIC GUIDE



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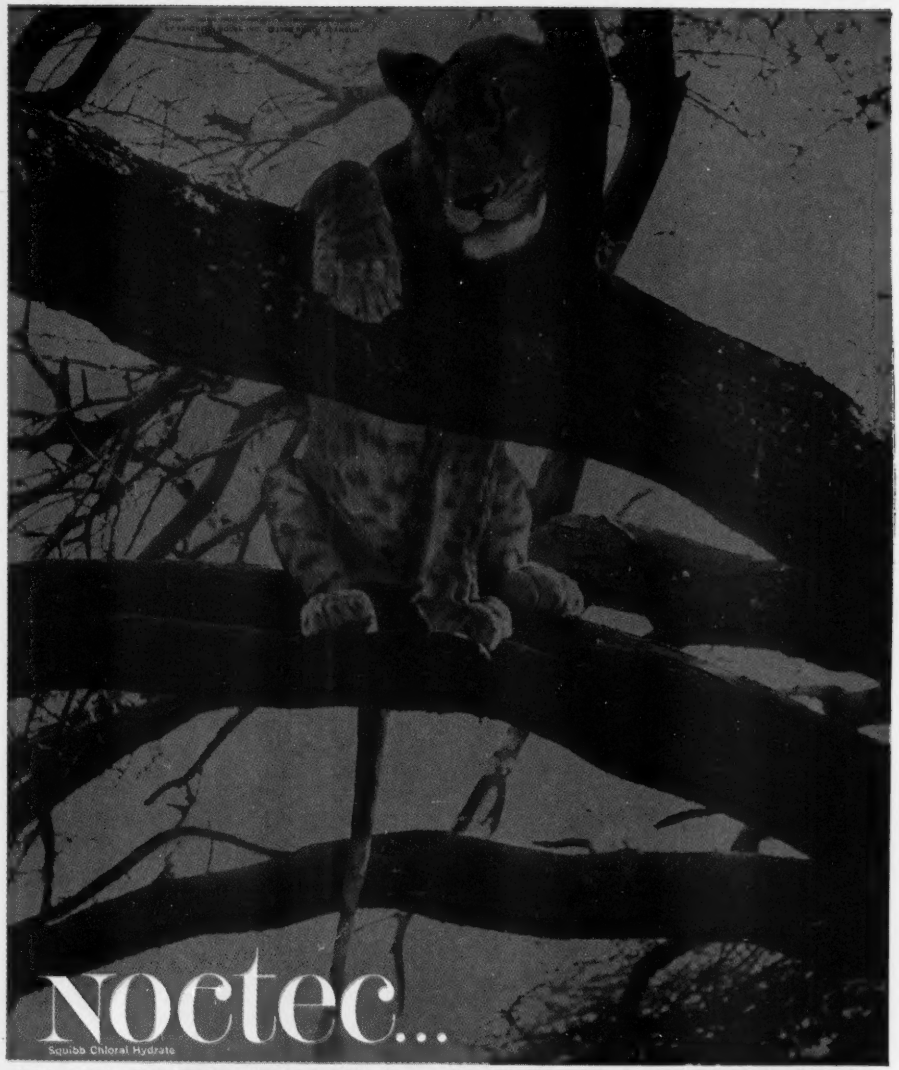
Gevrestin 77A
Prostall 70A



AND THE REST IS EASY! Noctec (Squibb Chloral Hydrate) invites refreshing sleep—gently, safely. Virtually free of side effects (including preliminary excitement or resultant "hangover" commonly observed with barbiturates), Noctec is conservative sleep therapy for patients of all ages. In recommended doses, Noctec may also be prescribed when heart disease or other illness is present • in psychiatric complications • during the first stage of labor • for pre- and postoperative sedation.

Dosage: Adults—1 or 2 500 mg. (7½ gr.) capsules or 1 or 2 teaspoonfuls of Noctec Syrup 15 to 30 minutes before bedtime. Children—for hypnosis—25 mg. per lb. of body weight; for sedation, 5 to 10 mg. per lb. of body weight.

Supply: 500 mg. (7½ gr.) and 250 mg. (3¾ gr.) capsules. Syrup, 500 mg., (7½ gr.) per 5 cc. teaspoonful.

'Noctec'® is a Squibb trademark.

For full information, see your Squibb Product Reference or Product Brief.

SQUIBB
Squibb Quality—the Priceless Ingredient

Only last year– the cancer patient in severe pain but strong enough to be ambulatory was often forced to be inactive because of the debilitating side effects of narcotic analgesics.

Winthrop LABORATORIES
New York 18, N.Y.

Today–pain can be relieved by a new potent analgesic that has little or no hypnotic effect–the same patient can stay on her feet and continue her day-to-day activities.

To help the ambulatory patient with cancer remain ambulatory

New Alvodine®

ethanesulfonate **Tablets**

Brand of piminodine ethanesulfonate

potent analgesia and alertness

Clinical results in more than 3000 patients show new Alvodine to be a real advance in the relief of pain – closer to "pure" analgesia than any drug yet developed. And here is a potent analgesic that is fully effective *orally*.

Alvodine tablets give ambulatory patients with cancer relief of pain as great as that obtained from morphine, but free of both the high incidence and severity of side effects associated with morphine.

Most patients with cancer who took Alvodine "... were able to carry on their normal activities such as shopping and house cleaning with marked freedom from their symptoms. Another advantage was the absence of other significant side effects such as constipation commonly encountered with use of other narcotic material, i.e., morphine and codeine."[1]

Because pain is relieved, appetite definitely improves[1] and weight loss is checked.

For the patient with cancer who requires parenteral analgesia, Alvodine can be injected subcutaneously or intramuscularly.

Alvodine tablets, 50 mg., scored. Usual adult dose: ½ or 1 tablet every four to six hours as needed.

Alvodine ampuls of 1 cc. containing 20 mg. per cc. Usual adult dose: from 0.5 cc. to 1 cc. subcutaneously or intramuscularly every four hours as needed. *Narcotic blank required.*

1. Molander, D. W.: Use of a new analgesic in patients with neoplastic disease, *Current Therap. Res.* 2:370, Aug., 1960.

digests from current literature

Deep Reflexes in Old Age

MAX ELLENBERG. J.A.M.A. 174: 468-469, 1960.

Knee and ankle reflexes unelicitable with reinforcement are pathologic signs regardless of age.

Although a rare healthy person may be devoid of deep tendon reflexes, loss of knee and ankle jerk is the most sensitive indicator of the state of the peripheral nervous system. With toxic neuropathy, knee jerks may disappear before any sign of motor or sensory paralysis is noted. Unless neurologic disease is overt, missing deep tendon reflexes usually reflect diabetic neuropathy.

When a patient holds his muscles tense, the reflexes may be obtained by distracting his attention. For persons needing increased tonus, reinforcement maneuvers are helpful. The knee jerk is reinforced by tapping the tendon at the moment the patient pulls his hooked hands apart. To reinforce the ankle jerk, the patient, with knees slightly flexed, presses the ball of his right foot against the examiner's hand.

Knee and ankle jerks were evaluated in 200 persons 65 years of age or older known not to have diabetes or overt neurologic disease. Reinforcement was necessary to obtain the reflexes in 20 per cent of the subjects, but only 1 per cent had reflexes lacking. Deep reflexes in 200 healthy adults 20 to 60 years of age were no easier to elicit without reinforcement; again, reflexes could not be elicited in only 1 per cent.

Cholecystostomy in the Aged

R. E. CONDON and L. M. NYHUS. Am. J. Surg. 100: 544-550, 1960.

Cholecystectomy is the definitive surgical treatment of cholecystitis, but cholecystostomy does have a place in the management of the disease in elderly or poor-risk patients. Cholecystectomy may subsequently be possible and advisable in many of these patients.

Surgical drainage of the gallbladder is seldom done for chronic cholecystitis. For the acute form of the disease, cholecystostomy (1) may be planned when the patient's age or debility or the extremity of a coexisting degenerative disease precludes cholecystectomy or (2) may be selected during operation when inflammation and edema so obscure the structures in the portal triad that adjacent structures may be injured if cholecystectomy is continued or when the patient's condition rapidly deteriorates.

Many postcholecystostomy patients will need cholecystectomy. Resection should be done as soon as possible after drainage, preferably within two months, in all patients who are reasonably good surgical risks or whose condition can be improved sufficiently through treatment of chronic degenerative diseases. Surgical resection of the gallbladder is especially necessary when choledochal or cystic duct stones have not been removed during cholecystostomy, because the risk of recurrent attacks is high. Patients who are poor surgical risks should be observed after the first operation and cholecystectomy performed if symptoms reappear. The operative mortality is increased in these patients, but the dangers of untreated, symptomatic biliary disease are greater. Patients who remain asymptomatic for over a year after cholecystostomy probably will have no further attacks, and resection need not be considered.

(Continued on page 32A)

relieves rigidity
and reduces muscle spasm
in the
parkinson patient

PHENOXENE™

a new synthetic compound

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*Doshay, L. J., and Constable, K.: Treatment of Paralysis Agitans with Chlorphenoxamine Hydrochloride, J.A.M.A. *170*:37 (May 2) 1959.

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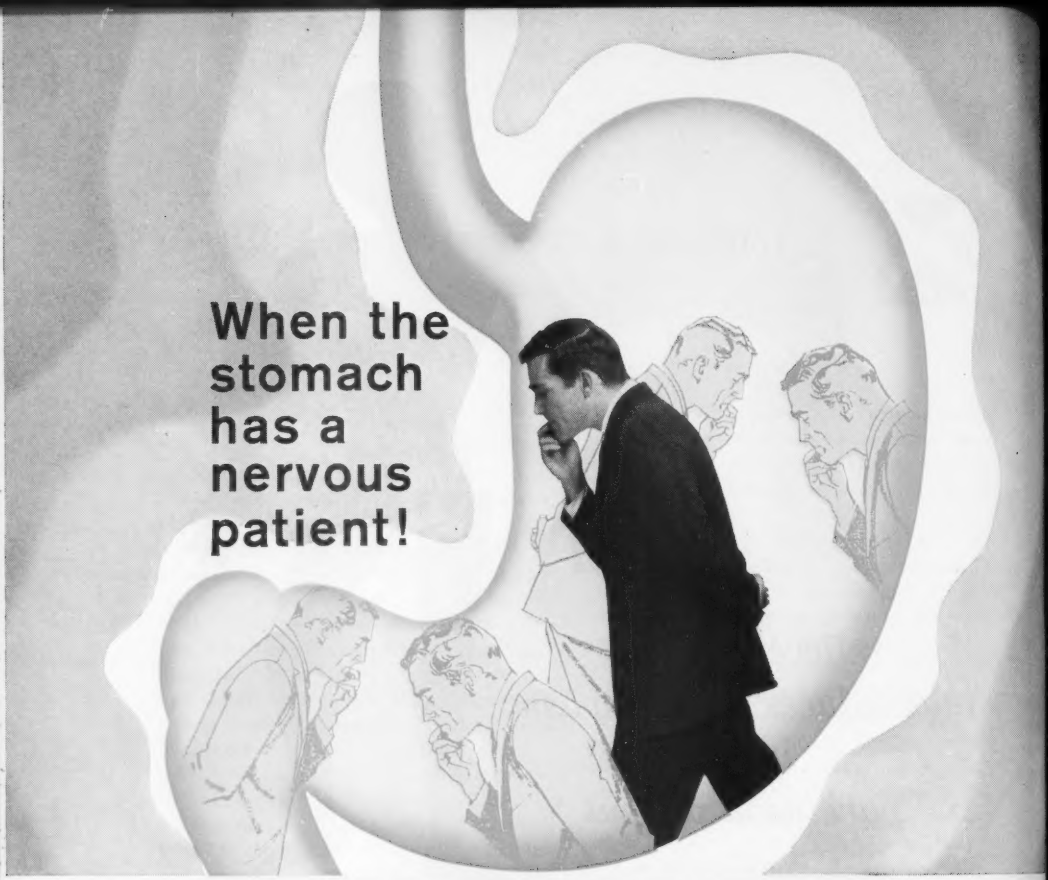

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antispasmodic/sedative

relaxes the tense patient and his jittery stomach... without the sedative "build-up" many patients experience with phenobarbital preparations.

BUTIBEL combines the "time-matched" components—BUTISOL SODIUM® butabarbital sodium 15 mg. and extract of belladonna 15 mg.—each having approximately 5 hours' duration of effect. Thus, with Butibel there is no overlapping sedation, no antispasmodic gap—t.i.d. dosage keeps the patient comfortable without inducing sluggishness.

Available as: BUTIBEL Tablets • Elixir • Prestabs® Butibel R-A (Repeat Action Tablets)

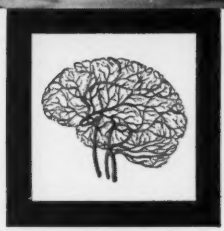
McNEIL McNEIL LABORATORIES, INC., Fort Washington, Pa.

✓ from mental confusion to the right frame of mind

✓ continuous, 24-hour cerebral oxygenation for the aging patient. By stimulating respiratory and circulatory function, GERONIAZOL TT* relieves mental confusion, depression, anxiety, and emotional instability—frequent problems in patients after forty—due to presenile changes in the vasculature of the brain. Notable benefit usually is seen within one to three weeks of therapy. It improves appetite, sleep pattern, and outlook—and GERONIAZOL TT* is non-hypertensive, non-excitatory.

Neither a tranquilizer nor a psychic energizer, GERONIAZOL TT* provides a physiologic stimulation of the cerebrum to permit the patient to adjust to his surroundings, become part of life itself again—and *attain the right frame of mind.*

References: 1. Curran, T. R., and Phelps, D. K.: Am. Pract. & Dig. Treat. *11:* 617, 1960. 2. Levy, S.: J.A.M.A. *153:* 1260, 1953. 3. Connolly, R.: W. Va. Med. J. *56:* 263, 1960.



Each TEMPOTROL contains: Pentylenetetrazol, 300 mg.; and Nicotinic Acid, 150 mg.

Indications: Respiratory and circulatory stimulant for the aged and debilitated with symptoms of mental confusion, depression, anxiety or arteriosclerotic psychosis.

Contraindications: None known in recommended dosage.

Dosage: One GERONIAZOL TT* tablet, b. i. d.

Supplied: Bottles of 42 tablets (3 weeks' treatment).

GERONIAZOL® TT*

*TEMPOTROL® (Time Controlled Therapy)

PHILIPS ROXANE, INC. Columbus 16, Ohio

Significant Postmenopausal Endometriosis

R. D. KEMPERS, M. B. DOCKERTY, A. B. HUNT, and R. E. SYMMONDS. Surg. Gynec. & Obst. 11: 348-356, 1960.

Endometriosis can be significant in postmenopausal women. It seldom is diagnosed because of the belief that after menopause the endometriotic process undergoes atrophy and clinical features gradually fade away. The continued activity in postmenopausal endometriosis is thought to be caused by the persistence of a significant level of estrogen despite menopause.

Approximately three-fourths of the lesions of significant postmenopausal endometriosis involve the ovary—the commonest site—or the intestine. A high incidence of intestinal endometriosis in patients with previous pelvic operations indicates that this condition may be a possible hazardous sequel to pelvic operations in women with endometriosis.

In 18 per cent of 136 postmenopausal women with external endometriosis established grossly or microscopically, clinically significant endometriosis was proved microscopically. The incidence reached 29 per cent with the inclusion of chocolate cysts that were strongly suspected of being endometriosis but were unverifiable microscopically. A preoperative diagnosis of endometriosis was made in only 2 of the patients with significant external endometriosis.

Approximately one-fifth of all patients with proved significant postmenopausal endometriosis exhibited histologic evidence of cellular activity in the ectopic foci. In none was the endometriosis symptomatic. In an additional study, endometriosis was found on the posterior uterine serosal surface in 7 of 50 necropsies on postmenopausal women.

Nephrocalcinosis: Effect of Unilateral Renal Trauma on the Contralateral Kidney of the Rat

MIKLOS NADASDI. J. Urol. 85: 13-16, 1961.

In rats, calcinosis does not appear in a well-developed endocrine kidney after treatment with dihydrotachysterol (DHT) plus Na_2HPO_4, even though calcification is intensified in the contralateral kidney. On the other hand, unilateral hydronephrosis or necrosis predisposes the affected kidney to calcification but does not alter the extent of calcification in the other. Since extreme neuromuscular stress, such as restraint, does not aggravate nephrocalcinosis produced by DHT plus Na_2HPO_4, aggravation of nephrocalcinosis by an endocrine kidney is caused by a specific mechanism rather than by a stressor effect.

When trauma was applied to the left kidneys of rats given DHT plus Na_2HPO_4, intensity of calcification in the intact kidneys depended on the type of lesion produced in the contralateral kidneys. The contralateral organ in a rat with an endocrine kidney was filled with large, rough calcium casts throughout the parenchyma, which caused serious tissue damage. Hydronephrotic and necrotic organs also were intensely calcified, but the contralateral kidneys in such rats, as well as in unilaterally nephrectomized animals, usually did not differ greatly from kidneys in treated but intact rats, which had slight tubular calcium deposition in the corticomedullary junction. Whether untreated or given DHT and phosphate, rats with endocrine left kidneys had similar degrees of calcification in the traumatized organs. In untreated animals with endocrine left kidneys, intact kidneys were not calcified, apparently because systemic calcifying agents were lacking.

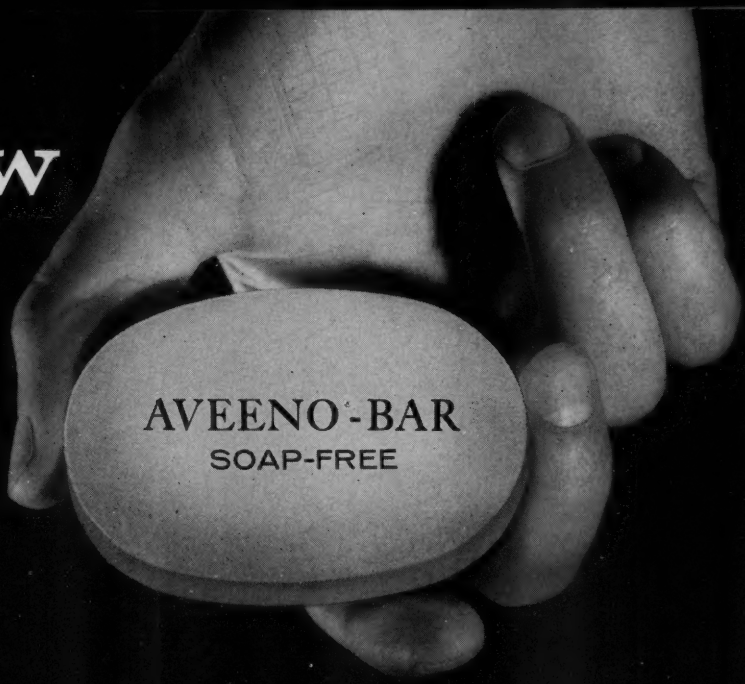
Evaluation of Oral Glutamate in Ammonemia due to Blood in the Gastrointestinal Tract

A. N. BESSMAN and G. S. MIRICK. Gastroenterology 39: 191-194, 1960.

Elevated blood ammonia levels, which are significant in the production of confusion and coma in serious liver disease and hepatic decompensation, can be lowered by intravenous administration of sodium glutamate. This is especially true when the ammonia intoxication results from blood in the gastrointestinal tract. However, oral administration of sodium glutamate is of no value in treating ammonemia due to blood in the gastrointestinal tract, and may be of no

(Continued on page 39A)

new



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- **ADJUSTED TO pH 5.7**
- **REDUCES CUTANEOUS PATHOGENS**

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INDUSTRIAL DERMATITIS • BATH ITCH
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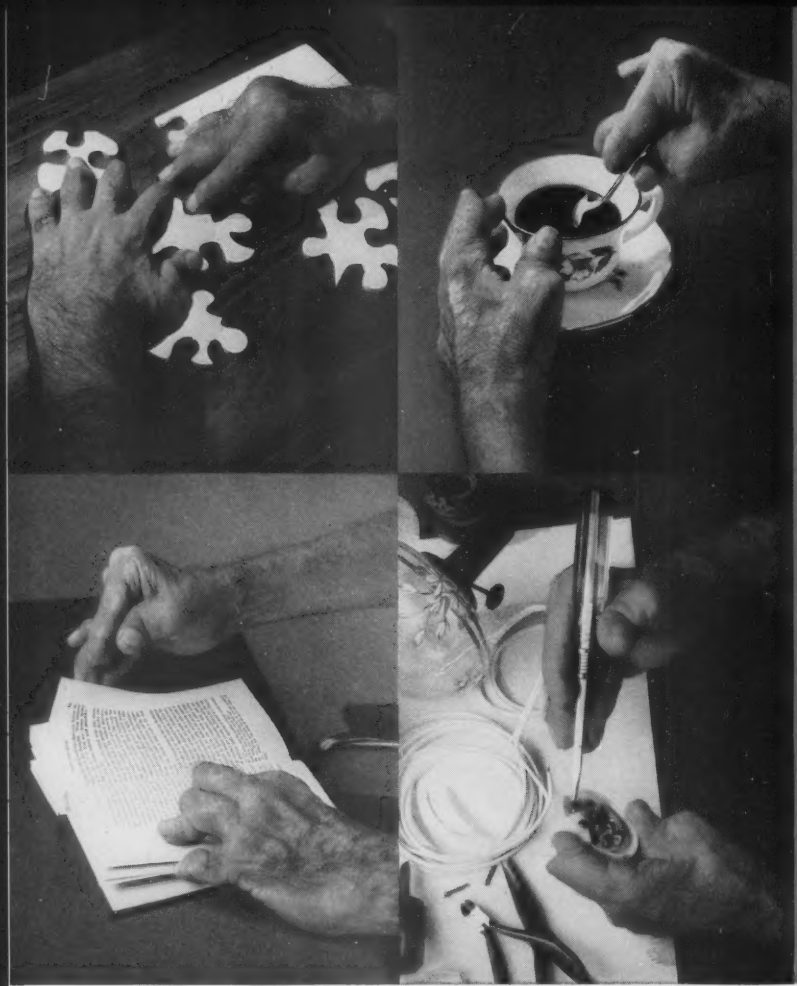

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Sodium salicylate (5 gr.) 0.3 Gm.
Sodium para-aminobenzoate (5 gr.) 0.3 Gm.
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When sodium should be avoided—

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Same formula as PABALATE-SODIUM FREE, plus hydrocortisone (alcohol) . . . 2.5 mg.

1. Barden, F. W., et al.: J. Maine M. A. 46:99, 1955.
2. Ford, R. A., and Blanchard, K.: Journal-Lancet 78:185, 1958.

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*Combes, F. C.: Ind. Med. & Surg. 30:29-34 (Jan.) 1961.

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Supplied: Tablets—containers of 12, 100, 500, and 1,000; Powder Packets—2.2-Gm. packets in boxes of 12 and 100; Bulk canisters of 4 oz., 13 oz., and 4 lbs.; Concentrated Solution—bottles of 4 oz.

References: (1) Sulzberger, M. B.; Wolf, J.; Witten, V. H., and Kopf, A. W.: Dermatology: Diagnosis and Treatment, ed. 2, Chicago, The Year Book Publishers, Inc., 1961, pp. 44-45. (2) Combes, F. C.: New York Physician & Am. Med. 33:3, 1949.

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Your Patients Can Enjoy Fine Foods With Minimum Diet Changes!

For good eating while maintaining serum cholesterol control

Leading authorities agree that where reduction of serum cholesterol levels is indicated, fat intake should not exceed ⅓ of total calories and of this, at least ⅓ should be polyunsaturated fats.

Polyunsaturated fats, such as those found in corn oil, are rich in the linoleates which are important in reducing serum cholesterol levels. This has been proven time and again in nutritional studies of hypercholesterolemia. Mazola Margarine and Mazola Corn Oil have outstanding P/S (polyunsaturate to saturate) ratios. Thus the hypercholesterolemic patient can usually enjoy the same appetizing foods as the rest of the family.

Mazola Corn Oil is unexcelled in polyunsaturates and lowest in saturates of all leading brands of vegetable oils. Mazola's P/S ratio is far higher than that of any other leading food oil. Your patient will find Mazola Corn Oil ideally suited for salad dressings and frying; also for baking wherever *liquid* shortenings are called for in the recipe.

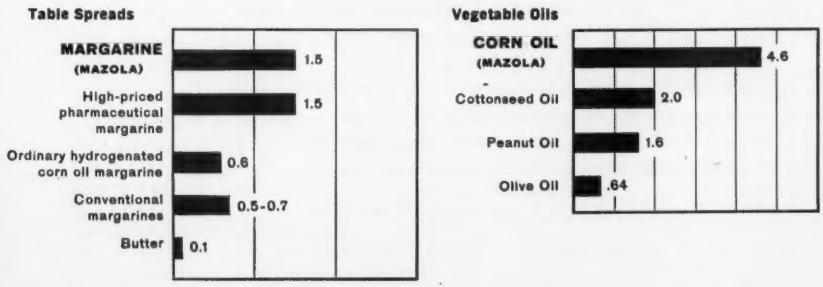
Mazola Margarine contains *liquid* Mazola Corn Oil as a major ingredient. This corn oil is not hydrogenated, thereby preserving its rich content of linoleates. Mazola Margarine contains 2 to 3 times as much natural linoleates as any other margarine readily available in grocery stores from coast to coast. Its taste, color and handling characteristics are unexcelled.

AVERAGE COMPOSITIONS OF MAZOLA® MARGARINE AND MAZOLA® CORN OIL
(All figures are in grams.)

	MAZOLA MARGARINE		MAZOLA CORN OIL	
	100 grams	2 oz. (4 tbsp.)	100 grams	1 fl. oz. (2 tbsp.)
Fatty Acids				
Polyunsaturated	21	12	51	14
Monounsaturated	40	23	32	9
Saturated	14	8	11	3
Natural Sitosterols	0.5	0.3	1	0.3
Natural Tocopherols	0.08	0.045	0.08	0.020
Cholesterol	none	none	none	none
Sodium	0.9	0.5	none	none

MAZOLA MARGARINE—410 Calories/2 oz.; Iodine Value—96
MAZOLA CORN OIL—250 Calories/fl. oz.; Iodine Value—124

RATIO OF POLYUNSATURATES/SATURATES
(Average values.)



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"and when you need a laxative..." Caroid and Bile Salts Tablets relieve temporary constipation without harsh, explosive action, through their unique, 3-way physiologic effect. (1) Caroid, a potent enzyme, aids protein digestion. (2) Bile Salts help overcome biliary stasis and increase the flow of necessary bile into the digestive tract. (3) A balanced combination of mild laxative ingredients stimulates peristalsis, helps restore normal bowel tone. Two tablets, taken at bedtime, will bring your patient gentle, effective relief next morning.

CAROID® & BILE SALTS TABLETS

American Ferment Division, Breon Laboratories Inc., New York 18, N. Y.

Refer to Page 543 — Physicians Desk Reference

benefit in ammonemia of hepatic decompensation in general.

Each of 6 patients with Laennec's cirrhosis received orally (1) blood containing a known amount of protein—a reliable method of elevating blood ammonia levels in stable cirrhotic patients, and (2) the equivalent amount of blood plus simultaneous oral administration of 25 gm. of sodium glutamate. After both tests, arterial and venous blood ammonia levels were followed over a five-hour period. The rise in blood ammonia levels after ingestion of the test loads was not prevented or diminished in a single patient by addition of oral sodium glutamate; in 2 patients, the levels rose more steeply and to greater heights with added glutamate. Ingestion by 2 patients of sodium glutamate alone also caused no significant change in blood ammonia levels. Slight evidence suggested that oral sodium glutamate may enhance the absorption of ammonia in gastrointestinal bleeding.

Postoperative Nausea and Vomiting. V. Antiemetic Efficacy of Trimethobenzamide and Perphenazine

J. W. BELLVILLE, I. D. J. BROSS, and W. S. HOWLAND. Clin. Pharmacol. & Therap. 1: 590-596, 1960.

Perphenazine (Trilafon) is more effective than trimethobenzamide (Tigan) or a placebo in preventing postoperative nausea and vomiting. Perphenazine has a sedative effect apparent ninety minutes after operation, while trimethobenzamide does not prolong sleeping time. Neither drug seems to produce a hypotensive effect.

Perphenazine appears to decrease the violence as well as the incidence of nausea and vomiting, the degree of effect being directly proportional to the size of the dosage. Trimethobenzamide prevents nausea and vomiting in patients who ordinarily would be slightly ill, leaving seriously upset cases unaffected.

A total of 1,055 patients was placed in 6 categories, depending on the type of anesthetic and whether surgery was intra- or extra-abdominal. Within the groups, 100 or 200 mg. of trimethobenzamide, 2.5 or 5 mg. of perphenazine, or a placebo was administered at random by the double-blind technic. A nurse gave the 1-cc. intramuscular dose upon the patient's arrival in the recovery room and observed the results every half hour for two and a half hours.

Incidence of postoperative nausea and vomiting after administration of trimethobenzamide was 12.1 per cent; after perphenazine, 6.5 per cent; and after a placebo, 14.2 per cent. Larger doses of the compounds did not produce significantly greater reduction in incidence than did lower doses.

Venous Stasis in the Lower Extremities

A. D. MC LACHLIN, J. A. MC LACHLIN, T. JORY, and E. G. RAWLING. Ann. Surg. 152: 678-685, 1960.

Thrombosis in the leg may begin as a result of venous stasis in valve pockets and in the venous saccules of calf muscles in the period of inactivity during and immediately after operation. Stasis appears to last longer in older patients, probably because of progressive distortion and dilation of the veins in the soleus muscle and general reduction in body activity. Elevation of the foot of the operating table seems to be the simplest and most effective single measure against stasis.

Venous stasis in the legs of about 100 patients who required intravenous pyelography but who had no disease of the peripheral arteries or veins or from any pelvic or abdominal obstruction to venous flow were studied by cineradiographic and rapid cassette-changer technics. In fifteen seconds, 25 cc. of 50 per cent diatrizoate was injected, after a 2-cc. initial dose, into a dorsal vein of the foot. The solution was directed into the deep veins by a tourniquet at the ankle.

In the group of 25 patients who remained in the horizontal supine position with the lower extremities quiet, dye was retained about nine minutes in the thigh channels and twenty-seven minutes in the leg pockets. In a group of 12 patients who voluntarily contracted thigh and leg muscles, the period of dye retention was about three minutes in the thigh channels and nine minutes in the

(Continued on page 42A)

CONCLUSIONS
of another clinical study[1] with
QUINAGLUTE®
DURA-TAB S. M.®
the only oral Sustained Medication* Quinidine Gluconate 5 gr. (0.33 Gm.)
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- effectively maintained normal sinus rhythm in almost all cases.
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For dosage, etc. REFER TO PDR Page 821

*U. S. Patent 2,895,881

1. Greif, E and Scheuer, J.: J Mount Sinai Hosp., Nov./Dec. 1960

Where's the arthritic this morning?

Thanks to Medrol Medules, he woke up comfortable and he's already on the go.

The first long-acting oral steroid, Medrol Medules gives the arthritic patient therapeutic action that continues through the night. In many cases, morning stiffness can become a thing of the past.

The slow, steady release of methylprednisolone often provides greater effectiveness, with less frequent administration and sometimes a reduced total daily dosage.

Many of your arthritic patients, too, can wake up comfortable on Medrol Medules.

Dosage: The following dosages are recommended in rheumatoid arthritis:

	Initial	*Maintenance*
Severe	12 to 16 mg.	6 to 12 mg.
Moderately severe	8 to 10 mg.	4 to 8 mg.
Moderate	6 to 8 mg.	2 to 6 mg.
Children	6 to 10 mg.	2 to 8 mg.

With Medrol Medules, it may be possible to reduce the total daily dose by ½.

Indications and effects: Medrol benefits (anti-inflammatory, antiallergic, antirheumatic, antileukemic, antihemolytic) have been demonstrated in acute rheumatic carditis, rheumatoid arthritis, asthma, hay fever and allergic disorders, dermatoses, blood dyscrasias, and ocular inflammatory disease involving the posterior segment.

Precautions and contraindications: Because of Medrol's high therapeutic ratio, patients usually experience dramatic relief without developing such possible steroid side effects as gastrointestinal intolerance, weight gain or weight loss, edema, hypertension, acne, or emotional imbalance.

As in all corticotherapy, however, there are certain cautions to be observed. The presence of diabetes, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, congestive heart failure, renal insufficiency, or active tuberculosis necessitates careful control in the use of steroids. Like all corticosteroids, Medrol is contraindicated in patients with arrested tuberculosis, peptic ulcer, acute psychoses, Cushing's syndrome, herpes simplex keratitis, vaccinia, or varicella.

Approximately 135 tiny "doses" mean smoother steroid therapy

Each capsule contains:
Medrol (methylprednisolone) 4 mg.
Supplied in bottles of 30 and 100.

Medrol* Medules*

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THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

leg pockets. When the foot of the operating table was raised, dye was retained two minutes in the thigh channels and five minutes in the leg pockets of 12 patients. The stasis-prolonging effect of age was noted in all groups but particularly in the group remaining in the horizontal supine position.

Newer Concepts of Amine Oxidase Inhibitors

ARTHUR L. SCHERBEL. Arch. Int. Med. 107: 37-42, 1961.

Amine oxidase inhibitors are valuable symptomatic agents possessing multiple pharmacologic actions and varied clinical effects. The commonly used drugs include: iproniazid phosphate (Marsilid), initial dose—not more than 50 mg. daily, maintenance dose 5 to 25 mg. daily; 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine (Marplan), initial dose—20 to 30 mg. daily, maintenance dose 10 mg. daily; α-methylphenethylhydrazine (Catron), initial dose—6 to 12 mg. daily, maintenance dose 3 to 6 mg. daily; phenelzine (Nardil), initial dose—15 mg. 2 or 3 times daily, maintenance dose 5 to 20 mg. daily; nialamide (Niamid), initial dose —100 to 300 mg. daily, maintenance dose 50 to 150 mg. daily; and tranylcypromine (Parnate), initial dose 20 to 40 mg. daily, maintenance dose 5 to 20 mg. daily. With any of these drugs, dosage must be individually controlled according to the patient's response.

The principal effects of amine oxidase inhibitors are: (1) increased psychomotor activity; (2) selective autonomic nervous system blocking with resulting postural hypotension, decrease in palmar perspiration, increased circulation to the extremities, constipation and urinary hesitancy; (3) lowering of pain threshold; and (4) acceleration of wound healing and of lesions of mesenchymal tissues.

Amine oxidase inhibitors are useful in the management of endogenous and senile depressions, and as supplemental therapeutic agents for the depressive reactions associated with chronic rheumatoid arthritis, chronic ulcerative colitis, and related diseases. The drugs have also been used for the relief of anginal pain, in the management of behavioral and emotional problems in children, in patients with advanced cancers or progressive chronic diseases, and, with oral diuretics, in the control of mild hypertension. Applied locally as a 5 to 10 per cent ointment, they exert favorable effects upon normal healing and mesenchymal ulcerated lesions, fistulas, and sinuses accompanying Raynaud's phenomenon, rheumatoid disease, and chronic ulcerative colitis.

Amine oxidase inhibitors potentiate the action of anesthetic agents, barbiturates, corticosteroids, ganglion-blocking agents, morphine, atropine and 4-aminoquinoline compounds. Chlorothiazide and hydrochlorothiazide potentiate the antidepressant and hypotensive effects of the amine oxidase inhibitors.

Although amine oxidase inhibitors have cumulative action, toxic manifestations are rare if patients are carefully observed. The first signs of toxicity are insomnia, constipation, and progressive postural hypotension. Acute liver necrosis occurs more frequently following excessive dosage or in patients with a history of liver disease. Iproniazid is more often the offending drug than the other amine oxidase inhibitors. Transient elevation of serum SGO transaminase is seen without evidence of liver damage. Rarely, unexplained anemia, leukopenia, itching maculopapular rash, and psychologic disturbances in the elderly are encountered. All these toxic manifestations disappear promptly when the offending drug is withdrawn.

Effectiveness of Anabolic Agents Nilevar and Colchicine in the Therapy of Patients Who Form Uric Acid Stones

F. W. LONGO and H. H. ZINSSER. J. Urol. 84: 766-770, 1960.

Nilevar or colchicine therapy in conjunction with a low purine diet may be more efficacious than diet alone in depressing twenty-four hour excretion of uric acid in persons with proved or suspected uric acid calculi. Patients with hepatic disease, ne-

(Continued on page 52A)

to correct constipation without whipping the bowel

DORBANE®

Tablets

For recurrent or chronic constipation in patients of all ages. A peristaltic stimulant acting through the blood stream specifically upon the intramural myenteric plexus of the colon. Motility of the small bowel not affected. Evacuation within 6 to 12 hours without cramping or griping. Each scored tablet contains 75 mg. of 1,8 dihydroxyanthraquinone.

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with added stool-softening effect

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Orange and Black Capsules

A dual-purpose bowel evacuant, combining the stool-softening effect of dioctyl sodium sulfosuccinate (50 mg.) with the non-griping peristaltic stimulation of Dorbane (25 mg.) in each capsule. This combination brings relief in "hard stools" constipation or fecal impaction.

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vertigo is reversible

Antivert® stops vertigo

moderate to complete relief of symptoms in 9 out of 10 patients[1]

Prescribe one ANTIVERT tablet (or 1-2 teaspoonfuls ANTIVERT syrup) 3 times daily, before each meal, for prompt relief of vertigo, Meniere's syndrome and allied disorders. Side effects are short-lived, usually only harmless flushing and tingling associated with vasodilation. As with all vasodilators, ANTIVERT is contraindicated in severe hypotension and hemorrhage.

Supplied: Small blue-and-white scored tablets (meclizine HCl 12.5 mg. and nicotinic acid 50 mg.) in bottles of 100. Syrup (each 5 cc. teaspoonful contains meclizine HCl 6.25 mg. and nicotinic acid 25 mg.) in pint bottles. Prescription only. Bibliography available on request.

Reference: 1. Scal, J. C.: Eye Ear Nose & Throat Month. **38**:738 (Sept.) 1959.

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NEOBON® Capsules
five-factor geriatric supplement

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Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being®

what TWISTON does for your allergy patient

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takes him out of this class: zzzzzzzzz zzzzzzzzzzzzzz zzzzzzzzzzzzzz

puts him into this class: !!!!!!!!!!!!!!! !!!!!!!!!!!!!!!!!!!!!!!!!!!!!!! !!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!

TWISTON is "tailor-made" to keep your allergy patient alert. Twiston is unsurpassed for symptom control. Twiston is effective in *unusually* low dosage: has a prolonged duration of action—drowsiness rarely occurs. No toxicity reported.

McNEIL U.S. PATENT PENDING

McNeil Laboratories, Inc., Fort Washington, Pa.

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...anti-allergic
...anti-side effects
available as:

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TWISTON, 2mg.
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(Repeat Action Tablets), 4mg.

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THIORIDAZINE HCl

provides highly effective tranquilization, relieves agitation, apprehension, anxiety

and "screens out" certain side effects of tranquilizers, making it virtually free of:

"The aim of current chemical, pharmacological, and clinical investigations of the phenothiazines is to find derivatives possessing potent and selective tranquilization with a minimum of toxic action.... In agreement with the published results of other investigators, we believe that thioridazine [Mellaril] shows a greater specificity of tranquilizing action and freedom from serious toxic effects when compared with some of the other phenothiazines."[1]

In the Menopause: A series of 150 menopausal patients were observed during Thioridazine (Mellaril) therapy for two years. The author states "The results were extremely good in those patients whose chief complaint was that of insomnia, tension, nervousness and, in general, the large group of menopausal symptoms that are due to disturbances of the psyche. The sense of 'well being' afforded these patients definitely decreased the intensity of 'hot flashes' and night sweats....Eighty-five per cent of patients complaining of insomnia, nervousness and irritability received excellent relief."[2]

Mellaril is indicated for varying degrees of agitation, apprehension, and anxiety in both ambulatory and hospitalized patients.

Usual starting dose: Non-psychotic patients – 10 or 25 mg. t.i.d.; Psychotic patients – 100 mg. t.i.d. Dosage must be individually adjusted until optimal response. Maximum recommended dosage: 800 mg. daily. Supply: Tablets, 10 mg., 25 mg., 50 mg., 100 mg.

1. David, N. A., Logan, N. D., and Porter, G. A.: Evaluation of Thioridazine (Mellaril), a new phenothiazine, in the hospitalized patient, A.M. & C.T. 7:364, June 1960. 2. Caldwell, W. G.: Emotional Disorders in the Menopause and Treatment with Thioridazine, presented at Bahamas Conference on Internal Medicine, Nassau, Bahamas, April 30-May 6, 1961.

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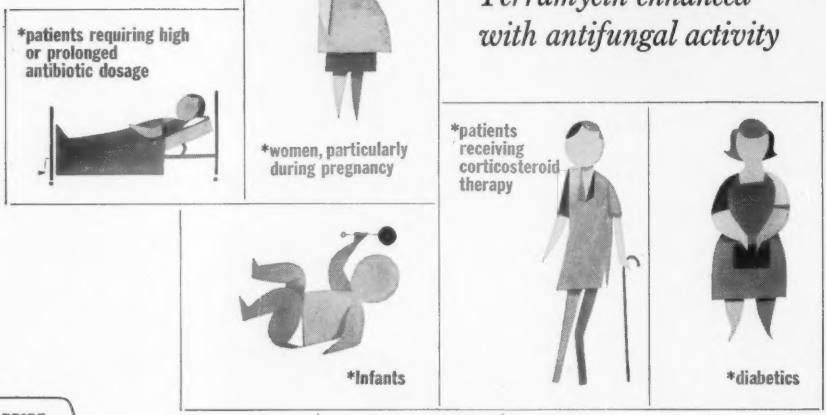
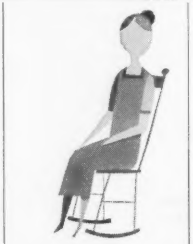
capsules and for oral suspension

the antibiotic effectiveness of Terramycin enhanced with antifungal activity





IN BRIEF

Cosa-Terrastatin provides the established antibiotic dependability of oxytetracycline (Terramycin®) with the potent antifungal activity of nystatin; inclusion of glucosamine enhances the absorption of Terramycin. Nystatin has a significant prophylactic action against monilial overgrowth.

INDICATIONS: Effective against both gram-positive and gram-negative bacteria, rickettsiae, spirochetes, large viruses, and certain parasites (amebae, pinworms), Cosa-Terrastatin is indicated in a great variety of infections due to susceptible organisms, e.g., infections of the respiratory, gastrointestinal, and genitourinary tracts, surgical and soft-tissue infections, ophthalmic and otic infections, and many others. The added protection afforded by Cosa-Terrastatin against monilial superinfection is especially important for those patients who are most likely to be susceptible to the overgrowth of *Candida albicans.*

ADMINISTRATION AND DOSAGE: Adults: Dosage providing 1 Gm. of oxytetracycline daily in four divided doses is usually effective. In *severe* infections, 2-4 Gm. daily may be indicated. Infants and children: 10-20 mg. of oxytetracycline per lb. of body weight daily.

SIDE EFFECTS AND PRECAUTIONS: If superimposed infection caused by resistant staphylococci is observed, the antibiotic should be discontinued, and a therapeutic trial of other antibiotics as indicated by susceptibility testing may be initiated. Aluminum hydroxide gel has been shown to decrease antibiotic absorption and is therefore contraindicated. Glossitis and allergic reactions are rare. Nystatin is virtually nontoxic and nonsensitizing; side effects are seldom observed. There are no known contraindications to glucosamine.

SUPPLIED: *Cosa-Terrastatin Capsules,* 250 mg. of oxytetracycline with 250 mg. of glucosamine and 250,000 units of nystatin, bottles of 50. *Cosa-Terrastatin for Oral Suspension,* each 5 cc. teaspoonful of reconstituted suspension contains 125 mg. of oxytetracycline with 125 mg. of glucosamine and 125,000 units of nystatin, 60 cc. bottles.

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Isordil "...appears to exert a more consistent and profound effect than any drug previously used for the prophylaxis of angina pectoris."[1] Rapid onset of action and prolonged effect are important advantages over other agents. "Benefits from [Isordil therapy] seemed to be more marked with continued use."[1]

Other studies have shown similar striking results.[2-7] With Isordil, you can expect a "...substantial reduction in frequency and duration of [angina] attacks."[2] Nitroglycerin requirements often can be drastically reduced or eliminated.

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References: 1. Albert, A.: Isosorbide Dinitrate in Treatment of Angina Pectoris, Journal Lancet 81:112 (Mar.) 1961. 2. Shapiro, S.: Angina Pectoris: Treatment with Isosorbide Dinitrate, Angiology 12:53 (Feb.) 1961. 3. Leslie, R. E.: Coronary Vasodilators—A Comparative Study, Western Medicine 2:56 (Feb.) 1961. 4. Russek, H. I.: Comparative Responses to Various Nitrates in the Treatment of Angina Pectoris, Journal of the Kansas City Southwest Clinical Society 36:14 (Dec.) 1960. 5. Berry, J. W.; Carney, R. and Lankford, H.: Clinical Experiences with Isosorbide Dinitrate (Isordil®), Angiology 12:254 (June) 1961. 6. Sherber, D. A. and Gelb, I. J.: The Clinical Pharmacology of Isosorbide Dinitrate: A Unique, New Nitrated Polyalcohol, **ibid.** 7. Joseph, L. G. and Mancini, A.: Isosorbide Dinitrate in Angina Pectoris, **ibid.**

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"...an active agent in restoring affected tissues to a state conducive to normal repair...."[4]

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References (1) Moss, N. H.; Morrow, B. A.; Long, R. C., and Ravdin, I. S.: J.A.M.A. **140**:1336, 1949. (2) Niemiro, B. J.: Journal-Lancet **71**:364, 1951. (3) Combes, F. C.; Zuckerman, R., and Kern, A. B.: New York J. Med. **52**:1025, 1952. (4) Lowry, K. F.: Postgrad. Med. **11**:523, 1952. (5) Diamond, O. K.: New York J. Med. **59**:1792, 1959.

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References: 1. Finkel, M. J.: M. Times 86:1391, 1958. 2. Doshay, L. J., and Boshes, L.: Postgrad. Med. 27:602, 1960. 3. A. M. A. Council on Drugs: New and Nonofficial Drugs 1960, Philadelphia, J. B. Lippincott Company, 1960, p. 264. COGENTIN is a trademark of Merck & Co., Inc.

MSD MERCK SHARP & DOHME Division of Merck & Co., INC., West Point, Pa.

phrotic syndrome, or nephrotic chronic renal disease should not receive Nilevar. Side effects, such as reversible depression of spermatogenesis, extreme chill, or impotency, may occur temporarily with Nilevar but are not associated with colchicine therapy.

Nilevar is given in doses of 10 mg. three to five times a day. Colchicine is given twice a day in 0.1 mg.-doses. Choice depends on efficacy in reducing uric acid excretion without toxic reactions. Fluid intake is maintained at 3,500 cc. per twenty-four hours. Sodium bicarbonate tablets, 1.2 gm. four times a day, are given to alkalinize the urine. Purine in the diet is limited to 120 mg. per day. During ureteral colic, Diuril in low dosage is used to block renal secretion of uric acid if a rise in serum uric acid can be tolerated.

Of 19 patients with uric acid calculi or calculi containing a high concentration of urate, 10 received Nilevar and 9 received colchicine therapy. In 9 of 10 patients receiving Nilevar, uric acid excretion was reduced an average of 556 mg. without a raise in serum uric acid levels. Colchicine treatment was equally effective.

Value of Serum Glutamic Oxalacetic Transaminase in Detecting Subclinical Liver Metastases

H. BADEN, H. ENGBERG, K. IVERSEN, and T. JAGT. Arch. Surg. 81: 608-610, 1960.

Serum glutamic oxalacetic transaminase (S-GOT) and serum alkaline phosphatase (SAP) are frequently elevated in the presence of liver metastases secondary to gastrointestinal carcinoma.

Metastases to the liver were found in 35 per cent of 37 patients with elevated S-GOT and in 12 per cent of 203 patients with normal preoperative determinations of S-GOT. When SAP was the preoperative test, 32 per cent of 82 patients with elevated values and 7 per cent of 147 patients with normal values had liver metastases.

Of 22 patients with elevations of both S-GOT and SAP, 55 per cent had liver metastases. Of 135 patients in whom both tests were normal, only 8 per cent had liver metastases.

Elevation of S-GOT, alone or combined with elevation of SAP, does not indicate liver metastases with sufficient certainty to affect the surgeon's judgment in determining the practicality of operation. However, in analyzing the indications for surgery in patients in whom the operative risk is great, normal levels of both S-GOT and SAP may support the surgeon's decision to operate, since these findings indicate that the chances are better than 90 per cent that no liver metastases are present.

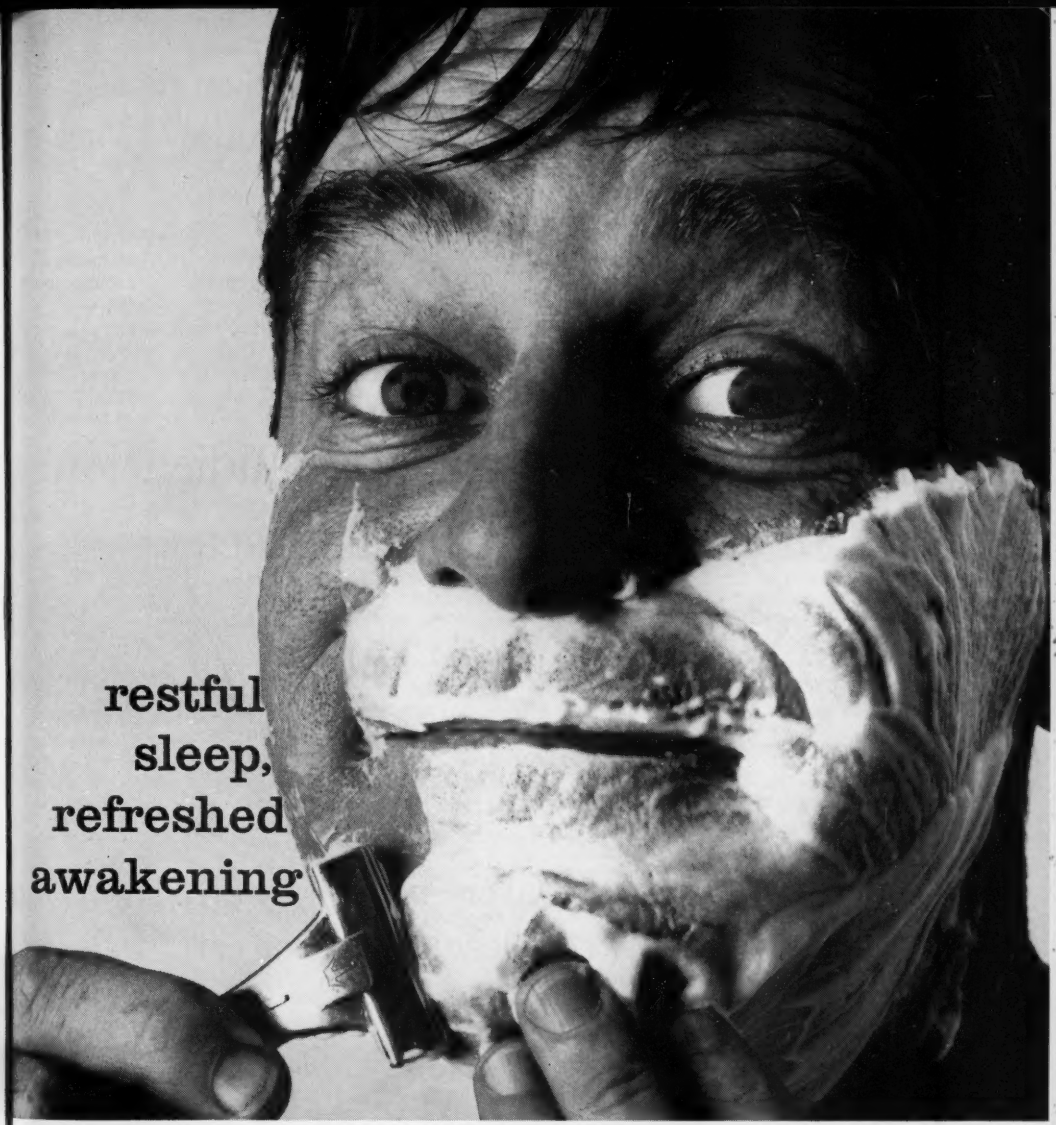
Prevention of Urinary Infection After Prostatectomy

A. MILLER, W. A. GILLESPIE, K. B. LINTON, N. SLADE, and J. P. MITCHELL. Lancet 2: 886-888, 1960.

The incidence of urinary infection after prostatectomy can be sharply reduced by destruction of bacteria in the urethra before operation and by exclusion of the organisms during and after surgery. Measures which are particularly effective in accomplishing this are (1) Disinfecting the urethra by instilling 5 cc. of 0.05 per cent chlorhexidine in glycerin for five to ten minutes immediately before surgery, (2) disinfecting nonboilable resectoscopes and cystoscopes in chlorhexidine, and (3) employing closed aseptic drainage and irrigation of the bladder.

The bladder should be irrigated promptly in the event of a hemorrhage immediately after surgery. Bleeding may lead to intractable obstruction by a clot, which will necessitate the removal and reinsertion of a catheter, thus increasing the danger of infection. If the catheter has to be replaced or a bladder syringe or evacuator used, the procedure should preferably be performed in the operating room, with full aseptic precautions.

The combined application of these precautionary measures in 2 hospitals reduced the incidence of urinary infection from 82 to 11 per cent of the 136 patients who had prostatectomy. About half of the infections which made up the residual 11 per cent were caused by the removal and reinsertion of catheters.



After a night of deep, refreshing sleep—this is the promise of Noludar 300. One capsule at bedtime acts quickly... eases your patient into sleep without pre-excitement, gives up to 6 or 8 hours of undisturbed sleep without risk of habituation, without toxicity or even minor side effects. Try Noludar 300 for your next patient with a sleep problem. Chances are he'll tell you

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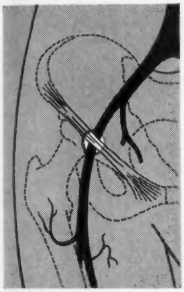
myo- -vascular relaxant

increases deep peripheral circulation by direct action
...without troublesome side effects

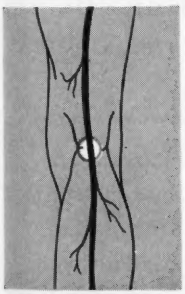
timing arterial bruit aids early diagnosis of collateral circulation in peripheral vascular disease

Purpose of the Test

This simple office or bedside procedure provides the physician with a diagnostic means for evaluating the adequacy of the collateral circulation bypassing an arterial obstruction. A good clinical correlation exists between a *continuous* arterial bruit, heard over a point of partial arterial obstruction, and inadequate collateral circulation.*



Site of femoral bruit over inguinal ligament.



Site of popliteal brut popliteal fossa.

Performance of the Test

Auscultate for bruit in the femoral triangle over the inguinal ligament, in the popliteal space, or over the axillary or brachial artery. *If a bruit is present, its duration in relation to the cardiac cycle is the significant finding.* If no bruit is heard when the patient is at rest, he should be exercised by running in place for a few minutes, or until he complains of claudication. Auscultation of the areas is then repeated, and the presence and timing of any bruits again noted.

Interpretation of the Test

Continuous bruit, audible throughout both systole and diastole, indicates poor collateral circulation.

Systolic bruit, heard only during systole, which remains the same or decreases following exercise, indicates good collateral circulation. Bruit heard only in systole with patient at rest, but which becomes continuous following exercise, or increases in intensity, suggests that collateral circulation is minimal.

Early estimation of the collateral circulation permits a more complete diagnosis of the arterial insufficiency. Treatment can thus be more accurately individualized—improving likelihood of a favorable response to therapy.

*Murdaugh, H. V., Jr., and McIntosh, H. D.: New England J. Med. *259*:1170-1171 (Dec.) 1958.

VASODILAN IS CLINICALLY EFFECTIVE[1-3]

The average "maximal walking distance, measured in 41 patients, more than doubled...during isoxsuprine [VASODILAN] therapy...."[1]

"Isoxsuprine hydrochloride [VASODILAN] was administered orally for a median period of seven months to 46 patients suffering from arteriosclerosis obliterans. Objective improvement could be demonstrated in 39 (about 85 per cent) of these."[2]

"With strictly a clinical office approach, isoxsuprine [VASODILAN] was used in the treatment of 100 patients with peripheral vascular disorders. Definite clinical improvement was obtained in 89 per cent of these patients."[3]

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In a study of 100 patients, "on an oral dose...no side effects have occurred."[3] "With oral administration, there are no contraindications."[1] "There were no significant side-effects or phenomena suggestive of the existence of contraindications."[2]

Contraindications: There are no known contraindications to oral administration of VASODILAN in recommended doses.

Cautions: VASODILAN should not be given immediately postpartum or in the presence of arterial bleeding. Parenteral administration is not recommended in the presence of hypotension or tachycardia. Intravenous administration is not recommended because of the increased likelihood of side effects.

Side effects: Few side effects occur when given in recommended oral doses. Occasional palpitation and dizziness can usually be controlled by dosage adjustment. Single intramuscular doses of 10 mg. or more may result in hypotension or tachycardia.

Dosage and administration: Oral—10 to 20 mg. (1 to 2 tablets) t.i.d. or q.i.d.; I.M.—5 to 10 mg. b.i.d. or t.i.d.

Supplied: 10 mg. tablets in bottles of 100; in 2 cc. ampuls containing 10 mg. (5 mg./cc.) for intramuscular use, boxes of 6.

For complete details on indications, dosage, administration, and clinical background of VASODILAN, see the brochure of this product available on request from Mead Johnson Laboratories, Evansville 21, Indiana.

References: (1) Kaindl, F.; Samuels, S. S.; Selman, D., and Shaftel, H.: Angiology *10*:185-192 (Aug.) 1959. (2) Samuels, S. S., and Shaftel, H. E.: J.A.M.A. *171*:142-144 (Sept. 12) 1959. (3) Clarkson, I. S., and Le Pere, D. M.: Angiology *11*:190-192 (June) 1960.

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Fuller, H. L.: Angiology *11*:200 (June) 1960.

Simple and safe for long-term therapy, Clarin* (sublingual heparin) effectively controls the prolonged postprandial lipemia associated with atherosclerosis by facilitating the normal physiologic breakdown of fats. Unlike parenteral heparin, the use of Clarin requires no clotting-time or prothrombin determinations. The antilipemic activity of each manufactured lot of tablets is confirmed by sublingual control tests in animals.

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An informative booklet, "Hyperlipemia, Heparin and Management of the Postcoronary Patient," is available from Thos. Leeming & Co., Inc., 155 East 44th St., New York 17, N. Y.

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Clarin

(sublingual heparin potassium, Leeming)

Geriatrics
VOLUME 16 NUMBER 8

SPECIAL ISSUE

Cardiovascular Diseases

RESEARCH INTO THE CAUSES of cardiovascular diseases and the clinical application of new knowledge in this field continues at an ever-expanding rate.

The editors of GERIATRICS present this special issue in an effort to provide up-to-date information on current investigations. They invited Jeremiah Stamler, M.D., Chicago, a national leader in the field of heart disease control, to serve as the guest editor of this issue.

He has selected the papers in this issue from among those presented at the thirty-third Scientific Sessions of the American Heart Association, St. Louis, October 21 to 23, 1960.

The encouragement of the AHA and the cooperation of the authors in connection with this undertaking is gratefully acknowledged.

The Editors

FOREWORD

Hypertensive and atherosclerotic cardiovascular diseases are the focal points of attention in most of the papers in this special issue. This emphasis was premeditated and deliberate. Among the dozens of excellent papers presented at last year's American Heart Association meeting, the guest editor purposively sought a selection emphasizing research on these problems. This action was based on two fundamental convictions: (1) that these are indeed the cardinal problems confronting cardiovascular research and practice today and (2) that a breakthrough against these diseases may be in the offing. Both of these conclusions, if valid, have important implications relating to direction, emphasis, and perspective for contemporary medical research and practice.

The clarification of the role of hypertension as a risk factor for atherosclerotic disease has served to deepen understanding of the hypertensive process itself, the interplay between these two diseases, and the factors contributing to the development of such complications as myocardial infarction and cerebral thrombosis, important causes of morbidity and mortality in hypertensive patients. Most dramatic of all to date, perhaps, is the development of a series of new pharmacologic agents for the effective control of hypertension. Particularly since the chlorothiazides were added to an armamentarium including rauwolfia preparations, hydralazine, ganglionic blocking agents, and so on, the ability to control mild and severe hypertension has become outstanding. And, as one of the papers in this issue indicates, the effects on long-term morbidity and mortality appear to be very significant. Hence the possibility of at least a limited early breakthrough against hypertensive disease.

The mere possibility of a breakthrough against hypertensive and atherosclerotic diseases is a tremendous achievement. *For the first time* in medical history, insofar as the major problems of chronic noninfectious disease are concerned, research has advanced far enough to pose the possibility of large-scale prevention and control. This accomplishment—skeptically denied by some, matter-of-factly accepted by others, acclaimed by but a few—deserves to be heralded, first of all because it is a unique and exciting leap forward for medicine. Irrespective of the final outcome, the elemental fact that the problem of preventing and controlling these diseases can be put on the agenda for possible practical solution indicates that a great barrier has been breached. This is a far cry from the intellectual atmosphere of only a few years ago, when these diseases were regarded by many as inevitable consequences of aging.[10]

The achievement needs to be heralded, in the second place, because it has a host of practical implications for both medical practitioners and investigators. For the former, it implies a marked change in approach to the practice of adult general and internal medicine. The concept that prevention

of disease and maintenance of health is a key task for the practicing physician is by now well established in obstetrics and pediatrics. To a large degree, obstetricians today are preoccupied with the management of normal pregnancy and the maintenance of optimal health pre- and postpartum. Correspondingly, pediatricians are extensively engaged in the supervision of healthy infants and children. Thus, preventive medicine is a conspicuous feature of their daily office practices.

This phenomenon does not as yet have its counterpart in the work of general practitioners and internists among adults. By and large, these key members of the medical profession are still overwhelmingly concerned with the care of the sick. But the possibility of a breakthrough against hypertensive and atherosclerotic diseases has a critically important implication with respect to this situation, for any effort to take advantage on a large scale of the possibility of preventing these diseases requires the periodic examination and long-term supervision of healthy adults. This is a *sine qua non* for the timely detection of signs of increased susceptibility and early occult disease. Only in this way does timely preventive intervention become possible, that is, the utilization of the multiple weapons now in the doctors' armamentarium—nutritional, hygienic, and pharmacologic—which may be of value in checking the development of gross illness and frank disability.

In emphasizing these implications for clinical practice of the possibility of a breakthrough against hypertensive and atherosclerotic diseases, the writer is fully aware of the over-all remaining uncertainties. Thus, it is not yet certain whether the available preventive measures can in fact significantly retard the development of overt clinical vascular disease. Although the accumulated research evidence points overwhelmingly in this direction, the definitive answer is yet to come. Five or ten years of hard work in mass field trials still lie ahead before an unequivocal answer can be expected.

Until such definitive data are collected, disagreements among scientists are bound to persist concerning the theoretic and practical significance of the research to date. This situation is virtually unavoidable for the present and immediate future. Such a phase has occurred with nearly every significant new advance in medicine. The important problem is to avoid disorientation amidst the continuing discussion and developing research. On the one hand, the disagreements are a product of indubitably important advances concerning hypertensive and atherosclerotic diseases—advances significant enough to indicate the possible value of new approaches to practical prophylaxis and therapy. On the other hand, the work is as yet unfinished. Definitive evidence from experimental-applied epidemiology and clinical investigation is not yet available. Incidence and mortality rates from hypertensive and atherosclerotic diseases have not yet been reduced by deliberate, controlled scientific intervention. Decisive efforts along these lines are being made, but their results are several years in the offing. From the aspect of clinical practice, therefore, the problem is one of a sound interim approach.

JEREMIAH STAMLER, M.D.

Hyperlipemia

BURTON S. SKLARIN, M.D.,
WINNIFRED SEEGERS, M.D., and
KURT HIRSCHHORN, M.D.
NEW YORK CITY

Persistent elevation of triglycerides is associated with coronary artery disease and may be familial or secondary to other diseases. These hyperlipemias are caused by a variety of abnormalities in the metabolism of triglycerides. Diagnosis and differential diagnosis of the hyperlipemia is relatively easy and is important in view of the possibility of successful therapy in preventing coronary artery disease.

BURTON S. SKLARIN *is research associate in the Department of Medicine,* WINNIFRED SEEGERS *is assistant professor and* USPHS *trainee in human genetics, and* KURT HIRSCHHORN *is assistant professor of medicine, New York University Medical Center. The last author is an Established Investigator of the American Heart Association.*

■ Hyperlipemia may be defined as an elevation of serum triglyceride, or neutral fat. Traditionally, the word hyperlipemia has been used to denote elevated triglyceride levels in the blood. Recently, terms such as hyperglyceridemia and hypertriglyceridemia have been suggested. We prefer to retain the name of hyperlipemia for states characterized by elevated serum triglycerides, with or without elevation of other serum lipid fractions. We would discourage its use for other disorders of lipid metabolism in which triglyceride levels are normal.

Some elevation of triglyceride may normally be seen after eating foods containing fat. Pathologic elevations may be primary, as in familial hyperlipemia, or secondary to other disease entities, such as diabetes mellitus, nephrotic syndrome, hypothyroidism, obstructive liver disease, pancreatitis, and von Gierke's disease.

Primary hyperlipemia was first described by Buerger and Gruetz in 1932,[1] and was shown to be familial by Holt and associates in 1939.[2] It is inherited as an incompletely dominant trait.[3] Incomplete dominance exists when the single dose of the gene for an abnormal trait—that is, the heterozygous condition—produces an abnormal effect which is less severe than that produced by the double dose, or homozygous condition. The homozygous form, with hepatosplenomegaly, abdominal crises, xanthoma, and grossly lipemic serum, occurs in infancy and childhood. It is relatively rare and is primarily of interest to the pediatrician. The heterozygous form fre-

quently presents with fasting hyperlipemia and xanthoma, especially of the eruptive type, but the only manifestation of the abnormality may be a delay in clearing ingested fat. This delay is found in individuals with secondary hyperlipemia but is invariably present in persons with primary or familial hyperlipemia, in whom it is the characteristic defect. The heterozygous abnormality is far more common than is generally believed and is frequently overlooked. The diagnosis may be made at any age if appropriate tests are performed. In a study of a young Swedish population,[4] the incidence of heterozygotes for hyperlipemia was found to be 2 to 3 per cent. We are currently engaged in a similar study on American students.

In view of recent reports stressing the association of hyperlipemia with coronary artery disease,[5,6] especially in relatively young men, detection of this condition is of prime importance. Hyperlipemia should be suspected if a patient has the onset of coronary artery disease before the fifth decade of life, xanthoma, elevated serum cholesterol, opalescent serum, or a family history of coronary artery disease. It may be useful to include a test for hyperlipemia as part of any complete screening examination in the course of which blood is drawn for other purposes, such as blood sugar or cholesterol tests. Many patients who have been diagnosed and treated as having primary hypercholesteremia have heterozygous hyperlipemia with secondary elevations of cholesterol. It is important to remember that hyperlipemia is a different disease from primary hypercholesteremia, in which there is no elevation of triglycerides. We feel that individuals with primary hypercholesteremia, with the exception of the rare, severely affected homozygote, are unaffected by their abnormal blood lipids and do not require treatment.[7,8]

Methods

Our methods of classification and differential diagnosis are based on our experiences with patients referred to us for one or more of the above reasons. The diagnosis of hyperlipemia is obvious when there is either an elevated triglyceride level—over 150 mg. per cent in our laboratory—or a serum optical density greater than 0.080 in a fasting specimen. There is good correlation between these two measurements in fasting, nonrefrigerated, nonhemolyzed serum.[9] Since 45 per cent of our hyperlipemics had a fasting optical density below 0.080, a better screening method is the examination of the patient's serum twelve hours after the ingestion of a high-fat meal. A normal adult will have cleared the fat from his blood by this time. It is important for the patient to have had a normal fat intake for several days before the test. For a more complete evaluation, we give the patient an abnormal load of fat and measure its disappearance from the blood. A fat tolerance test may be performed in the following manner:

1. The patient is given no food after dinner the night before the test.
2. A fasting blood specimen is drawn.
3. The patient is given a standard 90-gm. fat meal.
4. The patient fasts, except for water, until the test is finished.
5. Blood specimens, containing 10 cc. of clotted blood, are drawn at three-hour intervals for twelve hours after the fat meal.
6. The serum is analyzed for triglycerides by the method of Van Handel and Zilversmit[7] or the optical density is measured in a Coleman Junior spectrophotometer at 650 lambda.

Our standard meal consists of (1) 2 eggs, 1 oz. butter, 8 oz. milk, and 6 oz. heavy (40 per cent) cream, and (2) 2 slices of bread, dry cereal, coffee or tea, sugar, and salt. We use this meal as the

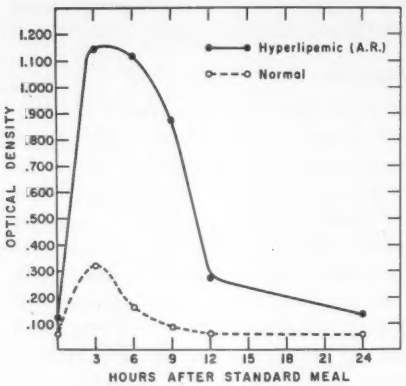

FIG. I. *Fat tolerance tests in normal and hyperlipemic patients.*

90 gm. of fat instead of using only concentrated fat or heavy cream, because pure fat may cause marked slowing of gastric contractility and delay in absorption or diarrhea with decreased absorption. When the fat is given in the form of dairy products in association with other foods, the meal is well tolerated.

A peak of lipemia is reached at about three hours, with the serum triglyceride and optical density returning to the fasting level from six to nine hours after the meal (figure I). In patients over 50 years of age, the return to fasting level may be delayed until nine to twelve hours after the meal. We consider it diagnostic of hyperlipemia when the patient, after normal absorption, does not clear his serum to his fasting level by nine to twelve hours, depending on age (figure I). Patients with hyperlipemia frequently show a much higher peak of lipemia coupled with the delay in clearing.

Ingested fat is absorbed and enters the blood stream predominantly in the form of chylomicrons. Lipoprotein lipase, which is activated in vivo by heparin,[10] catalyzes the breakdown of chylomicron triglyceride to free fatty acids.[11] These are then bound to albumin[12] and may be transported into the cells to be metabolized or may be resynthesized with glycerol to form the triglyceride fraction of lipoproteins (figure II).

In order to determine if a hyperlipemic patient can produce an adequate amount of functional lipoprotein lipase, we perform a heparin clearing test:

1. A fasting blood specimen is drawn.
2. The patient is fed the standard 90-gm. fat meal.
3. A specimen is drawn three hours after the meal.
4. 50 mg. of concentrated heparin is administered intravenously.
5. Specimens of blood are drawn fifteen and thirty minutes after heparin administration.
6. Chemical determination is done for triglycerides or serum optical density is examined at a wave length of 650 lambda in a 10-mm. cuvet.

The usual peak of lipemia is seen at three hours (figure III). Normally, following the injection of heparin, the optical density and triglyceride level fall promptly. We arbitrarily define heparin resistance as less than a 25 per cent decrease of optical density or triglyceride within thirty minutes of the injection.

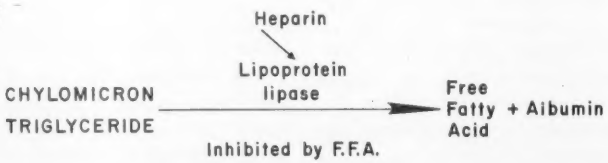

FIG. II. *Fat-clearing mechanism.*

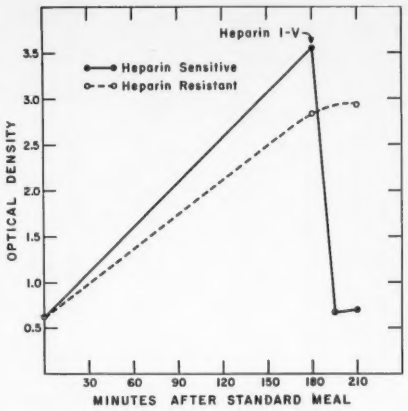

FIG. III. *Effect of heparin on alimentary lipemia in heparin-sensitive and heparin-resistant patients.*

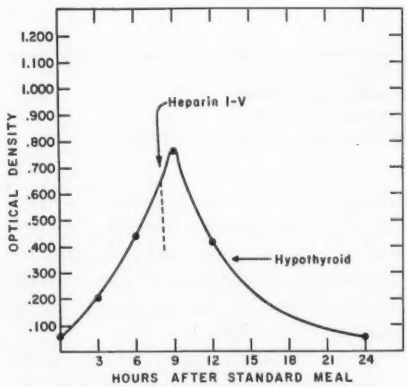

FIG. IV. *Fat tolerance and heparin tests in patient with hypothyroidism. The peak of the lipemia is reached as late as nine hours after the fat meal.*

On this basis, we classify our hyperlipemic patients as heparin-sensitive or heparin-resistant.

Differential diagnosis

We have studied several types of primary and secondary hyperlipemia by these methods. In the patient with untreated hypothyroidism, we frequently see a fasting lipemia, as well as slow absorption and clearing of fat (figure IV). The peak of lipemia is reached as late as nine hours after the fat meal. There is slow clearing, and the fasting level may not be reached until twenty-four hours after the meal. When heparin is given several hours after the standard meal, there is rapid clearing of the serum, with a drop of more than 25 per cent in thirty minutes. This would imply that there is an adequate amount of lipoprotein lipase present but that there is a defect in the normal activation of this enzyme, possibly due to a diminished amount or diminished activity of endogenous heparin (figure V, 3), leading to an elevation of serum triglyceride. Upon treatment with adequate doses of thyroid hormone, the fat tolerance returns to normal.

In the nephrotic syndrome, we may have lipemia in the fasting state or a delay in clearing an ingested fat meal. Several patients, although fasting triglyceride levels were normal, had both delayed clearing and relative heparin resistance (figure VI). Nephrotic patients have a deficiency of the serum

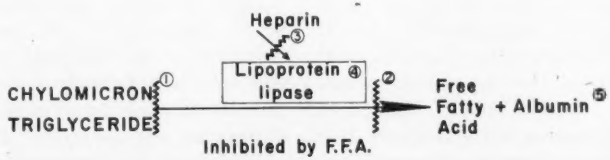

FIG. V. *Fat-clearing mechanism and sites of possible defects.*

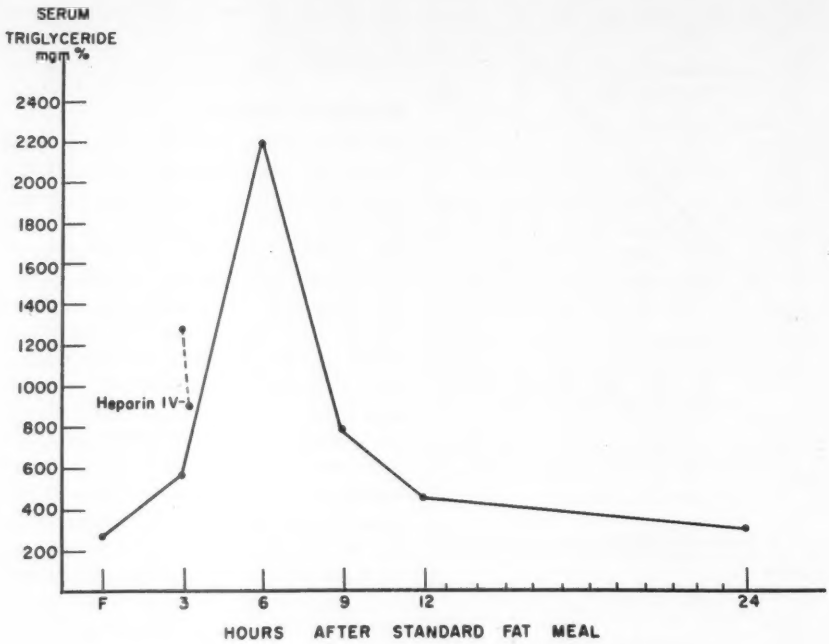

FIG. VI. *Fat tolerance and heparin tests in 50-year-old woman with nephrosis.*

albumin that is necessary for transport of free fatty acids (figure V, 5). When such acids accumulate, they have been shown to inhibit the clearing reaction.[13]

Fasting lipemia with or without a delay in clearing ingested fat may be present in uncontrolled diabetes. Suggested explanations for this lipemia include increased mobilization of fat, decreased production of adipose tissue, and a delay in clearing ingested fat.[14] However, the usual situation in uncontrolled diabetes is a high fasting level with normal clearing (figure VII) and a secondary rise at twenty-four hours, suggesting increased mobilization as the responsible mechanism. The lipemia should clear with adequate treatment of the diabetes. If it persists, the coexistence of essential hyperlipemia should be considered. In one patient (figure VIII), the delay in clearing when the diabetes was out of control was no greater than that produced by his primary hyperlipemia. The only difference observed was a higher fasting level of triglyceride.

If the patient's hyperlipemia is not secondary to these diseases, we make the diagnosis of primary hyperlipemia. Some individuals have been described in whom abnormal chylomicrons are present[15] and appear to be resistant to the normal clearing mechanism (figure V, 1). Ingested fat is absorbed and cleared normally. Although their fasting sera have a high optical density, these patients do not have essential hyperlipemia by our definition. There is no known association between this very rare entity and coronary artery disease.

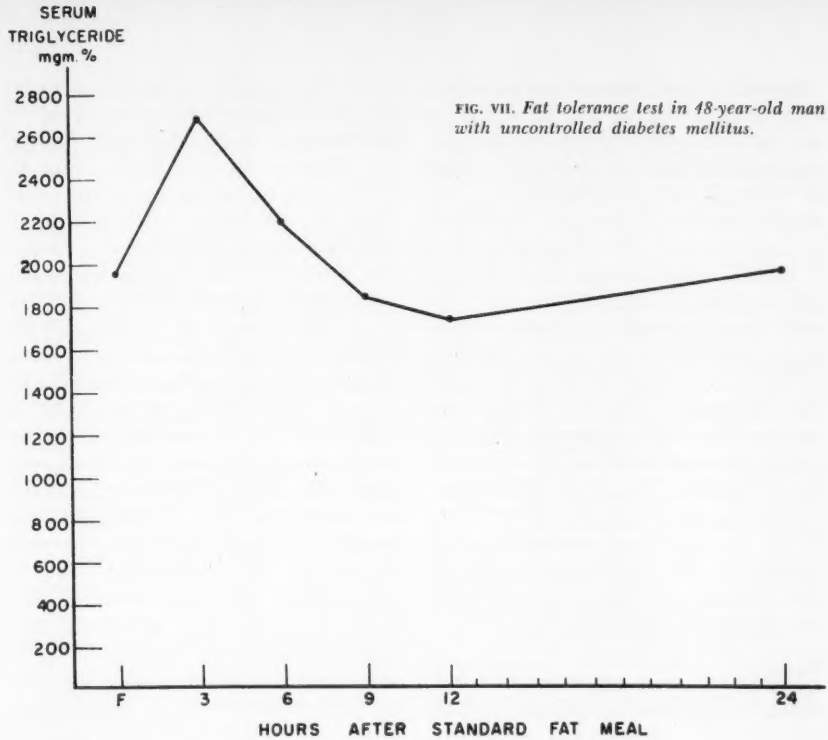

FIG. VII. *Fat tolerance test in 48-year-old man with uncontrolled diabetes mellitus.*

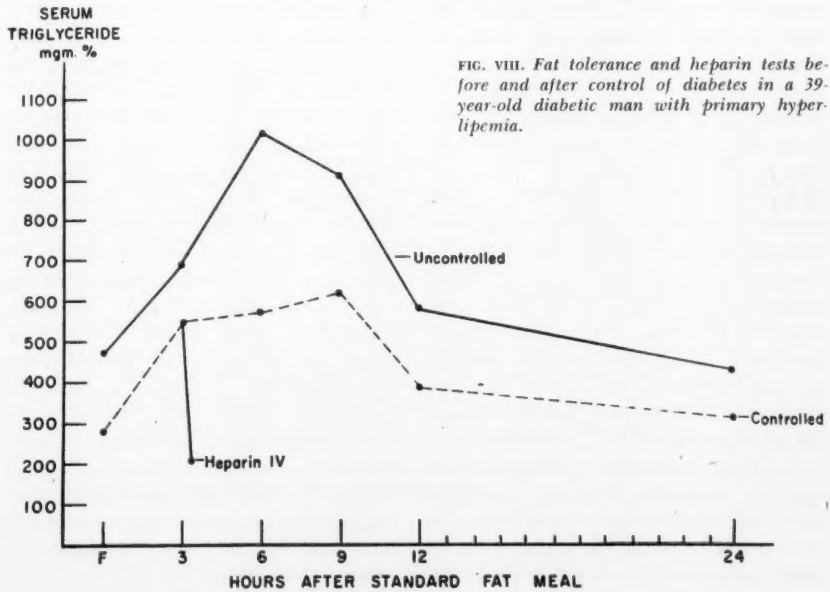

FIG. VIII. *Fat tolerance and heparin tests before and after control of diabetes in a 39-year-old diabetic man with primary hyperlipemia.*

Essential hyperlipemia can be subdivided into several entities according to the defect in the clearing mechanism. Hyperlipemic patients who have a delay in clearing and are heparin-resistant probably have a deficiency or abnormality of lipoprotein lipase (figure V, 4).[16] A small number of our patients with primary hyperlipemia fell into this category. Some investigators believe that these patients have an inhibitor of lipoprotein lipase (figure V, 2).[17] We could not demonstrate such an inhibitor in our patients when testing for it by the suggested methods. The large majority of our patients fell into the heparin-sensitive group (figure V, 3). It is not known whether these patients have diminished or abnormal mast cells, diminished heparin production, or an abnormal inactive heparin.

Therapy

Once we have located the defect, we are still left with the problem of therapy. Treatment should be begun in any patient in whom the diagnosis of hyperlipemia has been made, because of the association of hyperlipemia with early coronary artery disease. Postprandial hyperlipemia has been shown to be associated with development of electrocardiographic signs of myocardial insufficiency,[18] decreased coronary blood flow with diminished oxygen utilization by the myocardium,[19] inhibition of fibrinolysis,[20] and acceleration of blood clotting.[21] If a patient has constant hyperlipemia, these factors may play an important role in the etiology of coronary thrombosis. We believe that the discovery of hyperlipemia at a relatively early age and the institution of adequate therapy are important from a preventive point of view. Human lipoprotein lipase is not available for replacement in those patients who lack adequate activity of this enzyme. In heparin-sensitive patients, heparin therapy is expensive, inconvenient, and occasionally dangerous. Effective dietary therapy must be based on an understanding of the mechanism of the disease. Although lipids may be reduced initially by a fat-free diet, such a diet will eventually produce a starvation lipemia by fat mobilization.[22] Substitution of unsaturated for saturated fats achieves nothing so far as the elevated triglycerides are concerned.[23]

Spaced fat feeding, as described by Wilkinson,[24] is a practical method for controlling hyperlipemia. If the patients limit their fat intake to one meal a day and do not eat foods containing fat for breakfast or lunch, twenty-four hours is allowed for clearing the alimentary lipemia. Thus, each meal containing fat is eaten at a time when the serum lipids have returned to their fasting level. We have treated several patients in this manner with maintenance of normal lipid levels for prolonged periods.

If dietary therapy is not followed by the patient, or if it does not produce the desired results, we use nicotinic acid in doses of 3 to 6 gm. per day. We have been able to reduce serum triglyceride and cholesterol levels to normal values in most hyperlipemic patients, as we reported elsewhere.[25] In some individuals, the reduction of triglyceride has been associated with diminution or disappearance of angina, reduction in the size of xanthomatous lesions, and maintenance of good health over several years in individuals with several previous infarctions. Although we have no conclusive evidence that reduction of serum triglycerides will prevent coronary artery disease in susceptible individuals, we feel that lowering elevated triglycerides is a more logical approach to therapy than treatment of a secondary hypercholesteremia.

This study was supported by grants from the National Institutes of Health, United States Public Health Service (H2202), and from the American Heart Association.

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CURRENT OBJECTIVES in developing new steroids for the treatment of respiratory allergies are reduction of required steroid dosage and of mineralocorticoid and other unwanted side effects. The use of methylprednisolone with methoxyphenamine (Medrol with Orthoxine) showed predominantly satisfactory results in treating nearly 200 patients with bronchial asthma, allergic rhinitis, or both.

In most instances, the response to a given dosage of Medrol was improved when combined with the bronchodilator, Orthoxine, and the maintenance dosage of Medrol in the combination was lower than when Medrol alone was used. Cough control was excellent. Pulmonary function—as evidenced by total vital capacity and one-half second vital capacity—was improved in 46 of 48 patients submitted to measurement. No serious side effects were noted; minor side effects—mainly nervousness—occurred in fewer than 20 per cent of the patients.

W. C. GRATER: Effectiveness of methylprednisolone with methoxyphenamine in respiratory allergy. Ann. Allergy 18: 615-619, 1960.

Racial patterns of coronary heart disease

Blood pressure, body weight, and serum cholesterol in whites and Negroes

J. STAMLER, M.D.,
D. M. BERKSON, M.D.,
H. A. LINDBERG, M.D.,
W. MILLER, M.P.H.
and Y. HALL, M.S.
CHICAGO

Although Negro men have much more hypertension than whites, they do not have grossly higher rates for atherosclerotic coronary heart disease. Middle-aged low-income Negro men show lower prevalence rates for hypercholesterolemia, overweight, heavy smoking than whites. This may account for their coronary disease patterns, despite high prevalence rates for hypertension. Findings in Negro women are consistent with this hypothesis.

From the Heart Disease Control Program, Division of Chronic Diseases, Chicago Board of Health and the Department of Medicine, Northwestern University Medical School.

■ Available data on occurrence rates of hypertensive and atherosclerotic diseases in middle-aged American whites and Negroes present a challenging paradox. Thus, middle-aged Negroes, both men and women, undoubtedly have considerably more hypertensive disease than do whites (tables 1 and 2, figures I and II).[1-8] In the United States, hypertension is generally associated with increased rates of clinical coronary heart disease (CHD) in middle age.[1-10] Therefore, it might be anticipated that Negroes would exhibit considerably higher coronary heart disease rates than whites. Unfortunately, reliable statistics on this point are scarce. By and large, the limited available data do not reveal this expected finding. Some published reports indicate that Negroes have less CHD in middle age than do whites; others estimate that rates for whites and Negroes are essentially similar.[1-4, 11-41] Very few papers contain data suggestive of higher CHD rates for Negroes than whites, particularly insofar as men are concerned; limited evidence is available suggesting higher CHD mortality rates in middle-aged Negro women than in white women (tables 1 and 2, figures I and II).* [1-4, 26, 34, 35]

It was concluded that these contradictory and paradoxic findings merit

*The interpretation of Negro-white differences in CHD mortality is complicated by the excess number of Negro deaths assigned to the category, Degenerative Heart Disease (Code #422, International Statistical Classification of Diseases and Causes of Deaths, seventh revision) (table 1 and figure 1).[1-8]

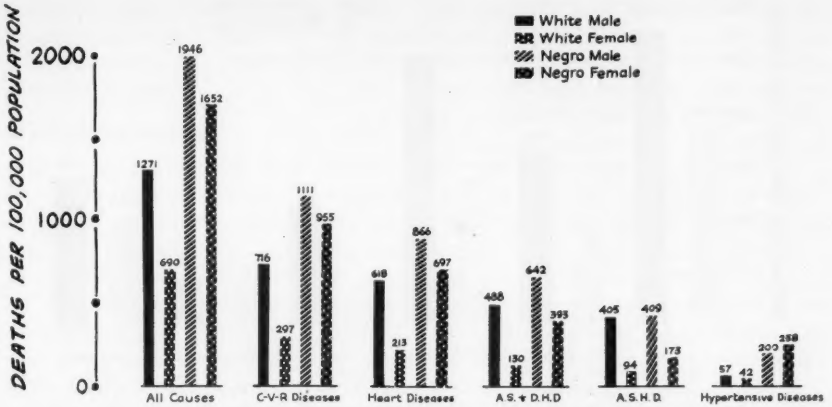

FIG. 1. *Death rates according to sex and race of persons 45 to 54 years of age, Chicago, 1951. C-V-R diseases = cardiovascular-renal diseases. A.S. and D.H.D. = arteriosclerotic and degenerative heart diseases (categories 420 + 422 in International Statistical Classification of Diseases and Causes of Death, seventh revision). A.S.H.D. = arteriosclerotic heart disease (category 420). Hypertensive diseases are categories 440 to 447.*

further study, particularly since their investigation might yield data clarifying aspects of the etiology of atherosclerotic coronary heart disease. It was recognized that several abnormalities, in addition to hypertension, may influence the incidence of clinical coronary heart disease—for example, hypercholesterolemia, obesity, diabetes mellitus, heavy smoking, and so on.[1,2,4,5,7,9,10] It was therefore

TABLE 1 **Age—Race—Sex Specific Death Rates* for Several Cardiovascular-Renal Diseases for Chicago Residents, 1951**

Cause	Race	Age-Sex 25-34 M	25-34 F	35-44 M	35-44 F	45-54 M	45-54 F	55-64 M	55-64 F
Arteriosclerotic heart disease	W	14	3	107	17	405	95	1,051	340
	NW	13	6	123	36	409	173	929	446
Arteriosclerotic and degenerative heart disease	W	20	4	137	30	488	130	1,278	460
	NW	51	29	210	116	642	393	1,457	899
Hypertensive heart disease	W	1	1	12	7	52	38	142	133
	NW	15	9	47	89	148	236	348	478
Hypertensive disease	W	2	1	15	8	57	42	152	145
	NW	17	18	69	114	200	258	389	504
Diseases of the heart	W	34	13	181	59	618	213	1,554	657
	NW	83	51	289	239	866	697	1,945	1,435
Cardiovascular diseases	W	41	15	205	80	693	288	1,779	854
	NW	100	78	363	329	1,078	916	2,450	1,996
Cardiovascular-renal diseases	W	47	19	213	85	716	297	1,822	891
	NW	111	91	382	342	1,111	955	2,525	2,098
All causes	W	168	99	483	276	1,271	690	2,989	1,634
	NW	487	337	883	735	1,946	1,652	4,261	3,054

*Deaths per 100,000 population. W—White. NW—Nonwhite.

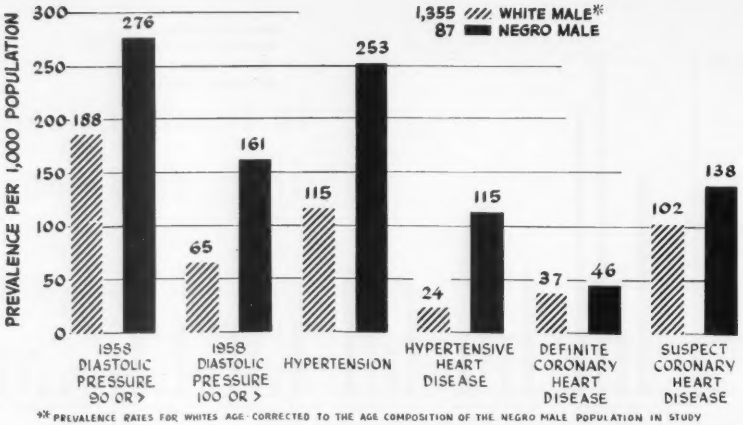

FIG. II. *Chicago utility company study, 1958, of hypertension, hypertensive heart disease, and coronary heart disease in white and Negro men aged 40 to 59. Prevalence rates for whites are age-corrected to age composition of Negroes. In this and subsequent figures, the differences in numbers of men—compared with the tables—reflect the fact that the figures were prepared before final data were available on all utility company employees. Note also that in figures II through IV the white males encompass both native-born and foreign-born, whereas in tables II through VI, white males aged 40 to 59 are exclusively native-born. The essential findings in the figures and tables are identical irrespective of these minor differences.*

TABLE 2 **Prevalence of Hypertension, Hypertensive Heart Disease, and Coronary Heart Disease in White and Negro Men, Age 40 to 59, Employed by a Chicago Utility Company, 1958 (Rates Per 1,000 Men)***

Number of men	Whites 1,065§			Negroes 93§		
All cardiovascular-renal diseases, including hypertension as sole finding	273	±	13†	433	±	50†
All cardiovascular-renal diseases, excluding hypertension as sole finding	133	±	10	253	±	48
All hypertensive disease	130	±	10	270	±	48
Hypertensive heart disease	31	±	5	107	±	32
Diastolic blood pressure 90 mm. Hg or >	220	±	12	299	±	49
Diastolic blood pressure 95 mm. Hg or >	103	±	9	210	±	44
Diastolic blood pressure 100 mm. Hg or >	76	±	8	158	±	40
Definite coronary heart disease	41	±	6	52	±	26
Suspect coronary heart disease	130	±	10	170	±	42
Mean systolic blood pressure (mm. Hg)	133	±	1‡	135	±	2‡
Mean diastolic blood pressure (mm. Hg)	82	±	<0.5	85	±	1

* All examinees in this analysis were native-born, and all rates are age-corrected to correspond to the U.S. male population, 1950.
† Standard error of prevalence rate per 1,000.
‡ Standard error of mean.
§ Number of men.

decided to approach the problem by collecting comparative data on these several parameters from middle-aged Negroes and whites.

Material and methods

Two population groups were surveyed, (1) white and Negro men employed by a Chicago utility company and (2) Negro men and women residing in low-income Chicago communities. The data on the utility company employees were obtained as part of long-term prospective epidemiologic studies of the total male labor force of this corporation, divided into 2 groups—ages 25 through 39 (approximately 1,500 men) and ages 40 through 59 (1,594 men).[5-8] Research on the men aged 40 through 59 was initiated on January 2, 1958, and on the men aged 25 through 39, on January 2, 1959. A complete medical examination was available in the company medical department on an annual (persons 50 through 59), biennial (persons 40 through 49), or quadriennial (persons 25 through 39) basis for all employees. It consisted of a thorough history and physical examination, 12-lead electrocardiogram, 6-meter posteroanterior roentgenogram of the chest, urinalysis, serologic test for syphilis, and serum cholesterol analysis as routine procedures, as well as other determinations of a special nature for epidemiologic research purposes. The complete medical record of each participant, including the periodic examination, was individually reviewed by the research group's internist (D.M.B.). At the same time, the current and all previous electrocardiograms were reviewed. The chest roentgenograms had been previously interpreted by a radiologist; his reports were utilized in arriving at a final definitive diagnosis. The criteria and classification of disease (definite and suspect) have been described previously.[5-7, 42-46] Definite hypertension was defined as a diastolic blood pressure of 95 mm. Hg or greater for most of the recorded readings in recent years. Borderline hypertension was diagnosed in individuals with diastolic levels of 90 to 94 mm. Hg. A diagnosis of hypertensive heart disease was made if there was diastolic hypertension plus electrocardiographic evidence of left heart strain, roentgenographic evidence of cardiomegaly, or both. Socioeconomic data were obtained from the personnel records of the entire group.

Of the 1,594 utility company employees aged 40 through 59, complete data were available on 1,466, or 92 per cent. Incomplete data were available on 128 men, some of whom were, by election, nonparticipants in the periodic examination program. Of the 1,466 examinees, 93 were Negro, all native-born; they were therefore compared with 1,065 native-born white men. Of the approximately 1,500 male utility company employees aged 25 through 39, data were available on a random sample of 38 Negroes and 492 whites aged 30 through 39; the white group included a few foreign-born.

The second source of data for this report was a survey of Negro residents of low-income Chicago communities. Through the cooperation of the Chicago Board of Health–United States Public Health Service Venereal Disease Detection Program, it was possible to obtain blood for serum cholesterol analysis on 1,430 men and women aged 25 through 64. Limited socioeconomic data were also collected, including place of birth, date of migration north if born in the south, employment status, occupation, and industry. Height and weight were also obtained by interview.

Serum cholesterol levels were deter-

mined in duplicate by the method of Abell and associates.[47] The ratio of measured or reported weight to desirable weight was calculated, using the life insurance tables for desirable weight for sex and height.[48]

Results

Occurrence rates of hypertensive disease and atherosclerotic coronary heart disease in the several age-sex-race groups. As already indicated, occurrence rates of hypertensive disease are considerably higher in middle-aged Chicago Negroes than in whites, irrespective of sex (tables 1 and 2, figures I and II). These data also indicate that coronary heart disease occurrence rates are at least as high in Chicago Negroes as in whites. The data on the male employees of the Chicago utility company suggest that Negro men in the 40 to 59 age range may have slightly higher coronary heart disease prevalence rates than do age-matched whites. However, the differences are not great (1.3-fold) and are not statistically significant in view of the small size of the Negro male group. The comparison of CHD in middle-aged Negro and white women, limited here to mortality data, suggests at least a two-fold higher rate in the Negroes.

Serum cholesterol levels in the several age-sex-race groups. Data on the age trend of serum cholesterol for the 4 major sex-race groups are shown in

TABLE 3

Age	White men, utility co. No.	Wt./Des. Wt.†	Cholesterol (mg. %)
25-29	—	—	—
30-34	171	—	213 ±
35-39	321	—	215 ±
40-44	282*	1.17	234 ±
45-49	266*	1.17	241 ±
50-54	301*	1.18	243 ±
55-59	216*	1.15	241 ±
60-64	—	—	—

* Native-born whites only.
† Wt./Des. Wt. is the ratio of reported or measured weight to desirable weight (from life insurance tables—cf. test).
△ Standard error of the mean.

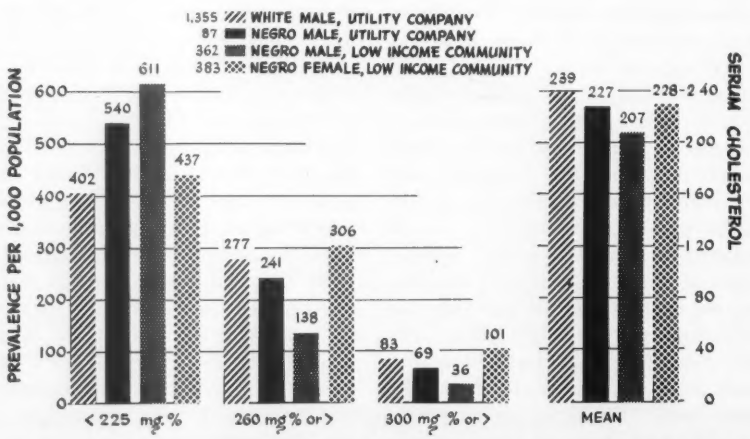

FIG. III. *Chicago utility company study and low income Negro community study, 1958, of serum cholesterol levels in Chicago whites and Negroes between the ages of 40 and 59.*

Mean serum Cholesterol Levels and Weights by Age and Sex in 4 Sex-Race Groups

Negro men, utility co.			Negro men, low-income community			Negro women, low-income community		
No.	Wt./Des. Wt.	Cholesterol (mg. %)	No.	Wt./Des. Wt.	Cholesterol (mg. %)	No.	Wt./Des. Wt.	Cholesterol (mg. %)
—	—	—	77	1.07	185 ± 4	91	1.06	187 ± 4
38	—	203 ± 7	78	1.10	205 ± 6	83	1.05	192 ± 4
			77	1.14	203 ± 5	103	1.11	196 ± 4
40	1.17	223 ± 7	90	1.07	208 ± 6	91	1.22	206 ± 5
24	1.13	226 ± 9	94	1.13	208 ± 4	102	1.28	223 ± 5
			92	1.15	205 ± 4	88	1.30	235 ± 6
29	1.19	229 ± 9	88	1.11	208 ± 4	102	1.31	233 ± 5
—	—	—	77	1.15	208 + 6	88	1.18	240 + 5

table 3 and figure III. For the utility company white men, mean serum cholesterol level rose with age from 213 mg. per cent at ages 30 through 34 to over 240 mg. per cent in the 40s and 50s. With respect to the Negro utility company employees, numbers are small and, therefore, the data must be interpreted with caution. At any given age, serum cholesterol levels appear to be slightly lower in these Negro men than in the white employees—for example, 203 mg. per cent compared with 214 at ages 30 through 39, and 229 compared with 242 at ages 50 through 59. Like the white men, these Negro men apparently exhibited a rise in serum cholesterol concentration with age. However, the plateau attained in the 40s and 50s seemed to be lower—less than 230 mg. per cent.

The Negro male residents of low-income Chicago communities had a somewhat different trend. They exhibited no rise in serum cholesterol levels beyond the 30 to 34 age period. Thereafter, serum cholesterol concentrations plateaued at values under 210 mg. per cent, sizably below those for both the Negro and, especially, the white male employees of the Chicago utility company. In contrast, Negro female residents of low-income Chicago communities exhibited a sizable rise in serum cholesterol levels with age. This increase was especially marked in the periods 40 to 44 and 45 to 49—that is, during the years of the menopause.

Age-specific data on the distribution of serum cholesterol levels for the 4 major sex-race groups of this study reveal (table 4) that, at all ages, the prevalence rates of normal serum cholesterol levels (less than 200 mg. per cent, or less than 225 mg. per cent*) were lowest in the white male employees of the Chicago utility company. This rate was considerably higher in the Negro men, particularly those in the low-income communities, in whom it remained relatively high at all ages. This rate declined steadily with age among the Negro women.

With respect to prevalence rates of hypercholesterolemia (260 mg. per cent or greater, 300 mg. per cent or greater) among the males, these were greatest for

*For discussion of the scientific basis for these cut-off levels for normal serum cholesterol see references 1 and 2.

the white employees of the utility company; they were only slightly less marked for the Negro employees of this company. In contrast, from age 40 on, rates of hypercholesterolemia were considerably lower—in the order of 50 to 65 per cent less—in the Negro male residents of the low-income communities (table 4). For the Negro women, at age 40 and beyond, the prevalence rates for hypercholesterolemia were high, tending to approach or exceed those for the white men.

Of the 93 Negro men 40 to 59 years of age employed by the utility company, 62 were identified as having had only one to eight years of education and were employed almost exclusively as semiskilled, unskilled, or service workers. The mean serum cholesterol for this group was 219 ± 6△ mg. per cent.

Of the 672 Negro men aged 25 through 64 in the low-income communities, employment status was obtained on 655; 246, or 37.6 per cent, were unemployed at the time of the survey in 1958. The mean serum cholesterol levels were 199 ± 3 and 206 ± 2 mg. per cent for the unemployed and employed men, respectively.

Body weights in the several age-sex-race groups. Mean values for the ratio of weight to desirable weight were similar in the Negro and white employees of the Chicago utility company, (table 3 and figure IV). The Negro men in the low-income communities tended to exhibit slightly lower mean values. From age 40 on, the Negro female groups from the low-income communities exhibited very high levels for this ratio, approaching or exceeding a mean level of 30 per cent above desirable weight in the years from 45 through 59.

Data on distributions of the ratio of observed weight to desirable weight in the several age-sex-race groups are presented in table 5. If a ratio of 0.95 to 1.04 is interpreted as indicative of desirable weight, then prevalence rates for this phenomenon were patently low for all groups.

Prevalence rates for moderate to marked overweight (ratio of weight to desirable weight of 1.15 or greater) and for marked overweight (ratio of weight to desirable weight of 1.25 or greater) were high for all sex-race groups. These prevalence rates were moderately lower for the Negro male groups from the low-income communities.

Prevalence rates of hypercholesterolemia and overweight in combination in the several age-sex-race groups. Prevalence rates for various combinations of

TABLE 4

Cholesterol	Age 30-39				Age 40-49
	White men utility co.	Negro men utility co.	Negro men low-income community	Negro women low-income community	Native-born white men utility co.
< 150	26.4	26.3	109.0	145.2	25.5
150-174	89.4	184.2	173.1	134.4	62.0
175-199	264.2	394.7	250.0	322.6	118.6
200-224	254.1	210.5	173.1	182.3	188.0
225-249	195.1	105.3	121.8	166.7	233.6
250-274	99.6	0.0	109.0	10.[illegible]	186.1
275-299	44.7	52.6	38.5	21.[illegible]	96.7
300-324	12.2	26.3	12.8	10.[illegible]	52.9
325 >	14.2	0.0	12.8	5.[illegible]	36.5
< 200	380.1	605.3	532.1	602.[illegible]	206.2
< 225	634.1	815.8	705.1	784.[illegible]	394.2
260 >	115.9	78.9	121.8	37.[illegible]	279.2
300 >	26.4	26.3	25.6	16.[illegible]	89.4
Total	492	38	156	186	548
Mean	215.1	202.5	203.6	194.[illegible]	237.4

△Standard error of the mean.

Distribution of Serum Cholesterol Levels in Several Sex-Race Groups at Different Ages (Rate Per 1,000)

	Age 40-49				Age 50-59			
	Native-born white men utility co.	Negro men utility co.	Negro men low-income community	Negro women low-income community	Native-born white men utility co.	Negro men utility co.	Negro men low-income community	Negro women low-income community
	25.5	78.1	76.9	108.8	15.5	69.0	77.8	31.6
	62.0	46.9	131.9	93.3	32.9	34.5	105.6	94.7
	118.6	156.2	236.3	207.3	112.2	103.4	227.8	163.2
	188.0	250.0	247.3	186.5	184.8	241.4	305.6	147.4
	233.6	125.0	181.3	160.6	234.0	275.9	161.1	210.5
	186.1	203.1	71.4	93.3	205.0	103.4	66.7	142.1
	96.7	78.1	22.0	98.4	121.9	103.4	33.3	105.3
	52.9	46.9	11.0	41.5	58.0	69.0	22.2	47.4
	36.5	15.6	22.0	10.4	36.8	0.0	0.0	57.9
	206.2	281.2	445.1	409.3	160.5	206.9	411.1	289.5
	394.2	531.2	692.3	595.9	344.3	448.3	716.7	436.8
	279.2	265.6	87.9	228.0	309.5	241.4	88.9	300.0
	89.4	62.5	33.0	51.8	94.8	69.0	22.2	105.3
	548	64	182	193	517	29	180	190
	237.4	224.1	207.6	214.8	242.2	229.4	206.5	234.1

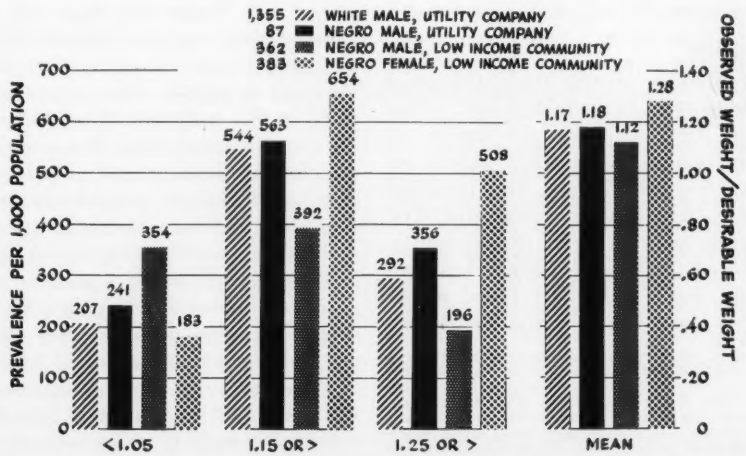

FIG. IV. *Ratio of observed weight to desirable weight of Chicago whites and Negroes between the ages of 40 and 59, 1958.*

hypercholesterolemia and overweight for the several sex-race groups are presented in table 6. The white and Negro men employed by the utility company exhibited similar prevalence rates for various combinations of hypercholesterolemia and obesity. The Negro women demonstrated an even higher prevalence rate for this particular set of defects at ages 50 to 59. In general, the Negro women in the 40 to 49 and 50 to 59 age groups, particularly the latter, tended to have the highest prevalence rates for the several combinations of the two abnormalities. In contrast, the Negro male residents of low-income communities consistently exhibited rates for the various combinations of hypercholesterolemia and overweight that were considerably lower than those for the 3 other age-matched sex-race groups.

For the utility company employees only, data were available on one other factor possibly influencing risk of coronary heart disease—heavy smoking.* Prevalence rates for heavy smoking were 444 ± 15△ and 286 ± 48 per 1,000 for the white and Negro men, respectively; the difference was significant statistically.

TABLE 5

Ratio: Wt./Des. Wt.*	Age 30-39				
	Native-born white men utility co.	Negro men utility co.	Negro men low-income community	Negro women low-income community	Native-born white men utility co.
< 0.95	—	—	103.2	279.6	69.3
0.95-1.04	—	—	264.5	209.7	155.1
1.05-1.14	—	—	303.2	172.8	215.3
1.15-1.24	—	—	116.1	161.3	270.1
1.25 or >	—	—	212.9	177.4	290.1
< 1.05	—	—	367.7	489.2	224.4
1.15 or >	—	—	329.0	338.7	560.2
Total	—	—	155	186	548
Mean	—	—	1.12	1.1	1.17

* Wt./Des. Wt. is ratio of observed weight to desirable w (from life insurance tables).

Discussion

The findings of this study on serum cholesterol levels in middle-aged urban white American men are similar to those presented in other recent reports.[1, 2, 4, 9, 49, 53] Before this investigation, virtually no representative data were available on serum cholesterol levels in sizable groups of adult American Negro men.† This study found significantly lower mean serum cholesterol levels and prevalence rates of hypercholesterolemia in low-income, middle-aged Negro men than in white men. The lowest values were observed in Negro men living in low-income communities, particularly those who were unemployed. The Negro men employed by a Chicago utility company had significantly higher values. However, their levels were not as high as those of the white men in this company. The gradations of serum cholesterol in the groups of middle-aged Negro men stratified by socioeconomic criteria suggest that environmental and not racial factors are the main causes of the generally lower serum cholesterol levels in the Negro men compared with the white. International epidemiologic data, demonstrating considerably lower serum cholesterol levels in Negroes in Africa, are consistent with this concept.[1, 2, 4, 54] (Here and elsewhere, reference is made to review sources with extensive bibliographies. The great research activity in this field has yielded

△Standard error of the prevalence rate per 1,000.
*Heavy smoking was defined as 20 or more cigarettes per day.
†One report of 63 Negro residents of Los Angeles, aged 40 to 59, gave a mean value of 249 mg. per cent, compared with a level for 503 age-matched whites of 265 mg. per cent. Socioeconomic data on the two groups were not included. This report also presented evidence on two small groups of Negro and white federal penitentiary prisoners.[51]

E 5

Distribution of Body Weights in Several Sex-Race Groups at Different Ages (Rate Per 1,000)

		Age 40-49			Age 50-59			
Negro women low-income commu	Native-born white men utility co.	Negro men utility co.	Negro men low-income community	Negro women low-income community	Native-born white men utility co.	Negro men utility co.	Negro men low-income community	Negro women low-income community
279.6	69.3	93.8	137.4	93.3	65.8	34.5	116.7	31.6
209.7	155.1	218.8	241.8	108.8	116.0	103.4	200.0	94.7
172.6	215.3	156.2	258.2	155.4	284.3	275.9	255.6	200.0
161.3	270.1	171.9	159.3	171.0	245.6	275.9	222.2	126.3
177.4	290.1	359.4	203.3	471.5	288.2	310.3	205.6	547.4
489.2	224.4	312.5	379.1	202.1	181.8	137.9	316.7	126.3
338.7	560.2	531.2	362.6	642.5	533.8	586.2	427.8	673.7
186	548	64	182	193	517	29	180	190
1.8	1.17	1.15	1.12	1.25	1.17	1.19	1.13	1.31

desirable w

a vast number of specific reports too numerous to include in any limited paper less than a review or a monograph in scope.) Further work is needed to test this hypothesis.

With respect to specific environmental factors possibly operating, only limited data are currently available. It has, of course, been extensively demonstrated that habitual diet is of key importance in accounting for different levels of serum cholesterol in different populations.[1, 2, 4, 54] However, virtually no information is availabe on comparative patterns of diet in urban United States Negroes and whites of different socioeconomic levels. The few published reports in this area present data on diet among American Negroes in the South, chiefly in southern rural areas. These studies indicate that southern Negroes ingest significantly less saturated fats and cholesterol than do whites.[55-57] Here again, there is urgent need for further research, particularly comparative studies of northern urban, southern urban, and rural population groups at different socioeconomic levels. The authors are participating in cooperative studies along these lines.[58-59]

A second variable, habitual physical activity, may be important in influencing lipid metabolism and serum cholesterol levels. In view of the occupational classifications of the Negro men evaluated in this study, particularly those residing in low-income communities, it may be reasonable to infer that, as a group, they are generally more active than the white utility company employees, whose occupations are classifiable as sedentary, light, or medium in habitual physical activity. However, detailed data are lacking on this parameter for the Negro residents of low-income communities. In any case, evidence in the literature suggests that level of habitual physical activity is a minor factor, particularly compared with diet, in determining levels of serum cholesterol in middle-aged male population groups.[1, 2, 4, 51, 52]

The serum cholesterol levels of the Negro women reveal a marked rise with age, particularly during the years of the menopause. (A discussion of the hormonal factors contributing to this phenomenon is beyond the scope of this paper.[4, 60, 61]) The values for serum cholesterol at different ages for these women are generally similar to those reported for white women in the United States. These concentrations for the Negro women are perhaps slightly lower for each age than those for white women, depending upon which data in the literature are used for comparison.[49, 51] It is, of course, recognized that limitations of interlaboratory comparability render such inferences tenuous. Nevertheless, the available data suggest that the race differential observed for men is not manifest for women. More studies are needed to evaluate this phenomenon further and to elucidate its mechanisms.

In this connection, the findings on body weight in the several age-sex-race groups may be relevant. The white men employed by the Chicago utility company manifest a high mean ratio of weight to desirable weight and high prevalence rates for both moderate and marked overweight. These findings are similar to those reported by other recent studies.[1,2,4,9,49,51] Previously reported data from the utility company epidemiologic study further demonstrate that a marked rise in weight occurs in these employees in the decades from young adulthood through middle age.[8] It is evident, therefore, that obesity is a highly prevalent phenomenon among middle-aged, employed, urban white American men. With respect to the small group of Negro men employed by the utility company, the data for this parameter are generally similar. However, in view of the possibility that the Negroes in this study were generally more active physically than the whites, it may be that their ratio of observed weight to desirable weight reflects greater muscle mass than in whites. In any case, the Negro men from low-income communities had lower mean values than the utility company employees for the ratio of observed weight to desirable weight and lower prevalence rates for both moderate and marked overweight. In view of the possibility that they, too, as a group have greater muscular development than the white men, this difference may assume greater significance.[52, 62]

The data on the Negro women indicate a marked gain in weight from young adulthood to middle age, resulting in very high mean values for the ratio of observed weight to desirable weight and very high prevalence rates for both moderate and marked overweight. These findings are in accord with the available data in the literature.[63] With re-

TABLE 6

	Age 30-39			
	Native-born white men utility co.	Negro men utility co.	Negro men low-income community	Negro women low-income community
Wt./Des. 1.15 or > and chol. 260 or >	—	—	71.0	26.1
Wt./Des. 1.25 or > and chol. 260 or >	—	—	38.7	0.0
Wt./Des. 1.15 or > and chol. 300 or >	—	—	12.9	16.1
Wt./Des. 1.25 or > and chol. 300 or >	—	—	12.9	0.0
Total	—	—	155	186

	Age 40-49			
	Native-born white men utility co.	Negro men utility co.	Negro men low-income community	Negro women low-income community
Wt./Des. 1.15 or > and chol. 260 or >	173.4	87.6	54.7	—
Wt./Des. 1.25 or > and chol. 260 or >	87.6	54.7	—	—
Wt./Des. 1.15 or > and chol. 300 or >	54.7	—	—	—
Wt./Des. 1.25 or > and chol. 300 or >	—	—	—	—
Total	548	284	84	84

Prevalence of Hypercholesterolemia and Obestity in Several Sex-Race Groups at Different Ages (Rate Per 1,000)

	Age 40-49				Age 50-59			
	Native-born white men utility co.	Negro men utility co.	Negro men low-income community	Negro women low-income community	Native-born white men utility co.	Negro men utility co.	Negro men low-income community	Negro women low-income community
	173.4	203.1	60.4	181.3	158.6	206.9	77.8	252.6
	87.6	125.0	16.5	134.7	94.8	103.4	33.3	210.5
	54.7	46.9	44.0	77.7	58.0	69.0	16.7	94.7
	—	—	16.5	57.0	—	—	11.1	89.5
	548	64	182	193	517	29	180	190

spect to this parameter, Negro women at present differ markedly from white women, who, among the 4 sex-race groups, manifest the lowest prevalence rates of overweight.

The findings on the prevalence rates for various combinations of hypercholesterolemia and overweight also reveal significant differences among the several age-sex-race groups. Thus, in middle age, the white male employees of the utility company and, particularly, the Negro women have high rates. In contrast, Negro male residents of low-income communities have significantly lower rates.

These data, together with the available information on the markedly greater prevalence rates for hypertension in Negroes, irrespective of sex, compared with whites, permit the formulation of a hypothesis concerning reported patterns of coronary heart disease occurrence in Negroes and whites. Thus, it has been demonstrated that risk of coronary disease in middle-aged men is related to such abnormalities as hypercholesterolemia, hypertension, overweight, diabetes mellitus, and heavy smoking. It has further been shown that various combinations of these factors—particularly hypercholesterolemia, hypertension, and overweight—are associated with markedly increased coronary susceptibility.[1,2,4,9] Based on this knowledge, it may be hypothesized that in Negro men, particularly low-income Negro men, the lower prevalence rates for hypercholesterolemia and obesity and the combinations of these abnormalities may result in their being protected against coronary disease and may operate to counter the greater susceptibility to coronary disease resulting from high prevalence rates of hypertension. The low prevalence rates of heavy smoking

may also contribute to this presumed effect. The lower prevalence rates of hypercholesterolemia, overweight, and heavy smoking may account for the fact that Negro men, despite higher prevalence rates of hypertension, manifest middle-age coronary heart disease rates similar to those of white men.

Limited data from other sources are consistent with this hypothesis. Thus, coronary heart disease occurrence rates in middle-aged Japanese and South Africa Bantu men are considerably lower than in middle-aged white American men, despite apparently high prevalence rates of hypertension. This relative infrequency of coronary disease is associated with low prevalence rates of hypercholesterolemia and obesity.[1,2,4] The animal experimental laboratory has also yielded data consistent with this evidence on man. Thus, experimental hypertension by itself does not, under any circumstances, lead to the development of atherosclerosis. However, in animals with diet-induced hypercholesterolemia, hypertension accelerates and aggravates atherogenesis.[4,60] All these data support the conclusions that serum cholesterol levels play a key role in the pathogenesis of clinical atherosclerotic disease and that hypercholesterolemia and hypertension act synergistically in this process.

The data on Negro women are also consistent with the foregoing hypothesis. In comparison with white women, Negro women have greater prevalence rates for hypertension, obesity, and diabetes mellitus and similar prevalence rates for hypercholesterolemia.[64] They would therefore be anticipated to manifest greater atherosclerotic disease occurrence rate in middle age. The limited available data indicate this to be, in fact, the case.

Further studies are needed to verify the findings of this study, to extend them to whites and Negroes of different geographic and socioeconomic origins in the United States, to elucidate the mechanisms responsible for the observed differences, and to clarify the differential patterns of coronary heart disease incidence. To accomplish this last objective, there is a particular need for prospective epidemiologic investigations.

Summary

1. Negro men and women in the United States have markedly higher rates of hypertensive disease than do whites.

2. Despite their status with regard to the hypertensive risk factor, middle-aged Negro men have coronary heart disease occurrence rates not significantly higher than those of white men; Negro women apparently have higher rates than white women.

3. Negro men, particularly those residing in low-income communities, have significantly lower prevalence rates of hypercholesterolemia and obesity, singly and in combination, than do middle-aged white men.

4. Middle-aged Negro women have higher prevalence rates of hypertension, obesity, and diabetes and similar prevalence rates of hypercholesterolemia compared with white women.

5. It is hypothesized that the observed rates of occurrence of coronary disease in Negroes, compared with whites, can be accounted for by the observed patterns in the 4 sex-race groups of such risk factors as hypertension, hypercholesterolemia, overweight, diabetes, and heavy smoking, singly and in various combinations.

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BOTH TOLBUTAMIDE and chlorpropamide appear to increase the fibrinolytic activity of the blood, although their mode of action is unknown. As there is no obvious correlation between the blood clot lysis times and blood-glucose levels, the observed increase of fibrinolytic activity does not seem to be a function of drug-induced hypoglycemia.

The behavior of chlorpropamide and tolbutamide merits further study (1) to determine whether either or both will enhance fibrinolytic activity for a long enough time to allow planned therapeutic assessment and (2) to discover the frequency and duration of the negative effects encountered with chlorpropamide.

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Changes in mortality rates of treated hypertensive patients in a decade

DERA KINSEY, M.D.,
HERBERT S. SISE, M.D., and
GEORGE P. WHITELAW, M.D.
BOSTON

Modern antihypertensive drugs apparently reduce the mortality rate for medically treated hypertensive patients, with the exception of women with moderately severe cardiovascular disease. The drugs do not seem to reduce the death rates for surgically treated patients. The mortality rates are lower for surgically than for medically treated hypertensive patients, however.

*All the authors serve on the staff of Massachusetts Memorial Hospitals and teach at the Boston University School of Medicine—*DERA KINSEY *as instructor in medicine,* HERBERT S. SISE *as assistant in medicine, and* GEORGE P. WHITELAW *as professor of surgery.*

The past decade has witnessed the introduction of a great many pharmacologic agents for the control of hypertension. The literature has provided an abundant number of short-term follow-up studies on the effect of these agents, but few data have been gathered on long-term follow-up studies of mortality rates.

Studies in the literature

Several series of patients with malignant hypertension, that is, with papilledema, have been reported, and the authors agree that the prognosis of patients with malignant hypertension is improved with treatment. Smirk[1] described a 61 per cent survival at four years and 37 per cent at five years of patients with malignant hypertension who had good or only slightly impaired renal function. Dustan and associates,[2] Bjork and associates,[3] and Harington and associates[4] reported similar results. Smithwick and Thompson[5] treated a number of patients by surgical methods and reported a survival rate of 50.5 per cent over a five-year period.

There is general agreement that the prognosis of maligant hypertension is improved by the use of antihypertensive agents. However, this is not the case when benign essential hypertension is

considered. Perera[6] followed 58 patients with essential hypertension for seven years. Half were treated with antihypertensive drugs and the other half were treated symptomatically only. During the period of observation, 16 patients in each group died, and there was no significant difference between the groups as to average survival.

Evelyn and associates[7] did an elaborate ten-year follow-up study in which they compared 100 sympathectomized patients with individually matched, symptomatically treated control subjects. The mortality rate at the end of ten years was 41 per cent for the surgical series and 47 per cent for the control series. They concluded that the over-all effect of the operation on morbidity and mortality was somewhat disappointing. It is pertinent to note that the sympathectomized patients of this series were the first to have this operation either by or under the direction of Dr. Reginald Smithwick. These operations were performed on the ward service at the Massachusetts General Hospital during the time the technic was being perfected. We do not feel that this group is a good sampling of the more than 3,000 patients who have had a lumbodorsal splanchnicectomy by the Smithwick group.

Dr. Paul Dudley White[8] did a ten-year follow-up study on 100 severe hypertensives—50 controls and 50 patients who had been treated by lumbodorsal splanchnicectomy. At the end of ten years, the mortality in the surgical group (50 per cent) was strikingly lower than that in the medical group (96 per cent).

Perry and Schroeder[9] made a study of four-year mortality rates of 209 medically treated patients with severe cardiovascular disease (Smithwick criteria groups III and IV). A comparison was made with comparable patients who were untreated and with surgically treated patients in groups III and IV. Both medically and surgically treated groups had lower mortality rates than did the group of patients with no treatment. There was no significant difference in the mortality rates for the treated patients.

Leishman[10] has recently reported a study in which he compared the mortality rate of untreated hypertensive patients with that of patients who have had medical treatment and others who have had surgical treatment. He concluded that the mortality was less among patients whose hypertension had been treated either by surgery or by drugs.

Material and methods

The present study was undertaken to show five-year mortality rates of hypertensive patients observed over a ten-year period. Actually, there were 10 groups studied for a five-year period each during this ten-year span—that is, the patients entering in 1944 were followed until 1949, those in 1945 to 1950, and so on. The years 1944 through 1954 were selected for this study because this allowed the best comparison of five-year mortality rates of hypertensive patients followed before and after the introduction of modern antihypertensive agents. While there was no analysis of these patients in respect to race, we believe the sampling was fairly random; less than 1 per cent were Negroes. During this ten-year period, 3,070 consecutive patients, who had a diastolic blood pressure of 90 mm. or over, were studied and grouped according to the Smithwick criteria.[11-13]

Smithwick criteria. The Smithwick criteria were designed to control as many of the variable factors as possible in an attempt to make the patient material in study groups as comparable as possible. Hagans and Brust[14] agreed with this plan. They found that, since there is

often marked lability in the diastolic blood pressures in patients in all stages of severity of essential hypertensive disease, evaluation of drug therapy should be based upon the degree of target organ involvement and optic fundal changes rather than solely upon the degree of elevation of the diastolic blood pressure.

TABLE 1 Numerical Value of Various Factors That Influence Prognosis

1	Cerebrovascular accident with or without minor residual Abnormal electrocardiogram Enlarged heart Impending congestive failure Phenolsulfonphthalein excretion less than 25 per cent in fifteen minutes or less than 60 per cent in two hours 50 years of age or older Mild angina
2	Cerebrovascular accident with residual* Frank congestive failure, moderate angina Phenolsulfonphthalein excretion less than 20 per cent in fifteen minutes† Unsatisfactory response to sedation
3	Phenolsulfonphthalein excretion less than 15 per cent in fifteen minutes†
4	Nitrogen retention

*Cerebral deterioration or definite involvement of arm and/or leg.

†Patients with phenolsulfonphthalein excretion of less than 15 per cent in fifteen minutes were omitted from this study for reasons given in text.

Example 1:	Abnormal electrocardiogram	1
	Cerebrovascular accident without residual	1
	Phenolsulfonphthalein excretion, 20 per cent in fifteen minutes	1
	Total (numerical grade of patient with hypertension)	3
Example 2:	Mild angina	1
	Abnormal electrocardiogram	1
	Enlarged heart	1
	Cerebrovascular accident with residual	2
	Total (numerical grade of patient with hypertension)	5

Classification in Smithwick groups. After a careful study of the cardiovascular system as a whole, a numerical value is assigned to various factors having a bearing on prognosis. These are summarized in table 1. The numerical values for each factor present are totaled, and this gives the numerical grade for the patient. Two examples of the method of numerical determination are given at the bottom of table 1. If the numerical grade is less than 4, the patient will be in group I or II; if the grade is 4 or more, the patient will be in group III or IV. The additional factors that determine the exact group of the patient are given in table 2. Thus, the patients in group I have persistently elevated blood pressure, with minimal or no eyeground changes and no abnormalities in the cerebral, cardiac, or renal areas. Those in the other groups have increasing amounts of cardiovascular disease.

A sedative test is done on all patients: 3 gr., or 180 mg., of amobarbital (Amytal) sodium is given by mouth at 7, 8, and again at 9 P. M., and readings of blood pressure are taken every hour from 7 P. M. to 7 A. M. The lowest reading of diastolic pressure during the sedative test is taken to be the response to sedation. To be regarded as satisfactory, the diastolic level during the sedative test should fall to (1) 90 mm. Hg or less in patients with resting levels between 100 and 119 mm. Hg, (2) 100 mm. Hg or less in patients with resting levels between 120 and 139 mm. Hg, and (3) 110 mm. Hg or less in patients with resting levels of 140 mm. Hg or more. Patients in both categories, surgical and medical, have been studied and classified in exactly the same fashion and can therefore be compared with respect to survival rates and mortality.

Exclusions from study. In this study, patients with a resting diastolic pressure

TABLE 2 Classification of Hypertensive Patients

Group	Numerical grade	Other factors
I	less than 4	Eyegrounds grade 0 or 1* No changes in cerebral, cardiac, or renal areas
II	less than 4	Eyegrounds grade 0 or 1, with changes in cerebral, cardiac, and/or renal areas. Eyegrounds grade 2, 3, or 4, with or without changes in cerebral, cardiac, or renal areas*
III	4 or more	Resting diastolic level below 140 mm. Hg Changes are present in cerebral, cardiac, and/or renal areas, but they do not include the following: cerebrovascular accident with marked residual; frank congestive failure; and phenolsulfonphthalein excretion below 15 per cent in fifteen minutes associated with a poor response to sedation
IV	4 or more	Resting diastolic blood pressure below 140 mm. Hg combined with one or more of the following: cerebrovascular accident with marked residual; frank congestive failure; and phenolsulfonphthalein excretion below 15 per cent in fifteen minutes combined with a poor response to sedation Resting diastolic level of 140 mm. Hg or more

*Eyegrounds are graded according to the criteria of Keith, Wagener, and Barker.

below 90 mm. were not included, because they were considered to be in the intermittent phase of hypertension and thus will be considered separately in another report. Of the total group, 114 patients, or less than 4 per cent, were lost before the end of the five-year period and therefore were excluded from this study. During the study period, every effort was made to diagnose and eliminate the patients with so-called curable hypertension; thus patients who had either renal or adrenal disease responsible for their hypertension were also eliminated. Although a few such diagnoses might have been missed, especially among the earlier cases studied, it is highly unlikely that this is a significant number.

Comparison of groups. The surgically treated patients in groups I, II, and III were considered to be comparable to the medically treated patients in the same groups. The medically treated patients in group IV, however, were more severely ill as a whole than were the surgically treated patients in group IV. This difference was primarily due to the difference in kidney function. In order to select group IV medical and surgical patients who were comparable, all patients with a phenolsulfonphthalein excretion of below 15 per cent in fifteen minutes were excluded from this study, thus eliminating 33 patients from surgical group IV and 148 from medical group IV.

A total of 2,775 patients remains to be examined (table 3). Of these, 1,642 were treated by lumbodorsal splanchnicectomy (sympathetic trunks D8 to L1, in addition to the greater splanchnic nerves, were removed bilaterally) and 1,133 patients chose nonsurgical treat-

TABLE 3 2,775 Patients* with Sustained Hypertension Followed Between 1944 and 1954

Groups	Surgical	Medical
I and II	1,189 (72.5%)	802 (71.0%)
III and IV	453 (27.5%)	331 (29.0%)

*Total number of patients studied and grouped according to Smithwick criteria and followed five years.

ment. Less than 20 per cent of all patients fell in group I or IV. Group I patients had virtually no cardiovascular disease and group IV patients had severe cardiovascular disease, without noteworthy uremia and, as previously stated, without a phenolsulfonphthalein excretion of less than 15 per cent in fifteen minutes. By far the largest group of patients, almost two-thirds, were in group II, having a relatively mild degree of cardiovascular disease. Group III was the second largest group, comprising approximately 25 per cent of patients, with moderately severe cardiovascular disease. In our method of grouping, the patients with malignant hypertension were not treated separately but were scattered throughout the groups, with the exception of group I, from which they were excluded by the procedure used for classification.

The 4 groups are shown in figure I, which divides the patients into sex, the year first studied, and the treatment received. Both medical and surgical groups were comparable throughout the study period as to total patients studied each year and group distribution.

Medical treatment. Veratrum began to be generally used for the treatment of essential hypertension in 1948,[15] although it had been used many years before as therapy in toxemia of pregnancy. The blocking drugs were introduced in 1949-1950 with hexamethonium,[16,17] and hydralazine[18] was introduced in the same year. Rauwolfia, including reserpine, appeared in 1951-1952.[19] Chlorothiazide was not released until 1957, but the patients seen first after 1952 would have had exposure to this drug by the end of their five-year follow-up periods. After 1950, the major-

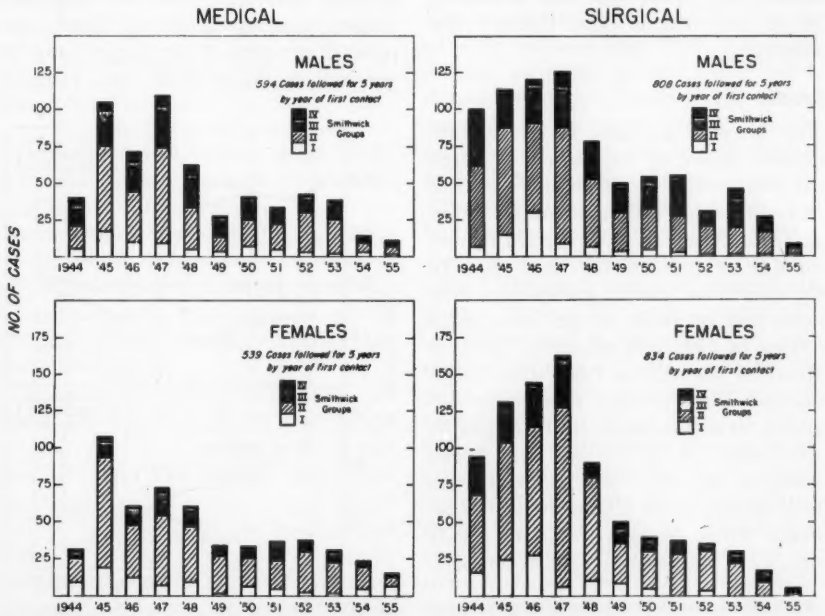
MEDICAL
SURGICAL
MALES
594 Cases followed for 5 years by year of first contact
MALES
808 Cases followed for 5 years by year of first contact
FEMALES
539 Cases followed for 5 years by year of first contact
FEMALES
834 Cases followed for 5 years by year of first contact
Smithwick Groups
IV
III
II
I
NO. OF CASES
1944 '45 '46 '47 '48 '49 '50 '51 '52 '53 '54 '55

FIG. 1. *Medically and surgically treated hypertensive patients, 1,133 and 1,642, respectively, divided according to sex, year first seen, and Smithwick criteria.*

ity of the medically treated patients, as far as we can determine, received one or more of the new antihypertensive drugs with or without dietary restriction. About 80 per cent of the medically treated patients were followed by a referring physician, and the other 20 per cent were treated by our group.

Selection of treatment. Selection of the treatment was made by the patient after the available types of therapy were discussed and explained to him. Before 1950, 67 per cent of the patients chose surgical treatment. After 1950, 53 per cent chose surgical treatment. Virtually none of the surgical patients before 1950 had additional drug therapy, although, in a few instances, supplementary dietary measures were used. After 1950, about 25 per cent of the surgical patients had some form of drug therapy, another 25 per cent had some form of dietary restriction, and the remaining 50 per cent had no other therapy than surgery.

Results

The five-year mortality in all patients, divided according to medical or surgical treatment, is shown in figure II. The mortality rates are recorded by three-year smoothing* in order to have a larger number of patients for each year. In the medically treated group, the mortality rate of about 40 per cent began falling in 1949 and reached a level of about 25 per cent in 1951, where it remained. The mortality rate in the surgically treated patients, which originally was about 10 to 15 per cent, began rising at the same time and reached a level similar to the medically treated patients. These changes would be highly significant if the groups were comparable. To exclude the possible effect of sex and degree of cardiovascular disease, the material was broken down into groups and sex. Figure III shows the five-year mortality rates in men and women of groups I and II. These comprise 72 per cent of the surgical and 71 per cent of the medical cases. Most of

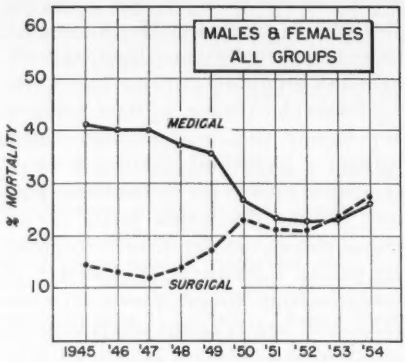

FIG. II. *Five-year mortality rates, with three-year smoothing, for all patients studied. Year indicates when patient was first seen and percentage indicates mortality at end of five-year period.*

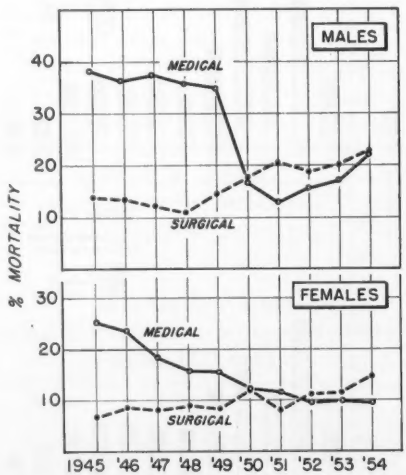

FIG. III. *Combined five-year mortality rates, according to sex, with three-year smoothing, of patients in Smithwick groups* I *and* II.

*Three year smoothing is done by pooling the deaths for three years to obtain a death rate for the middle of the three years. For the next year we drop one and add one, continuing thus throughout series.

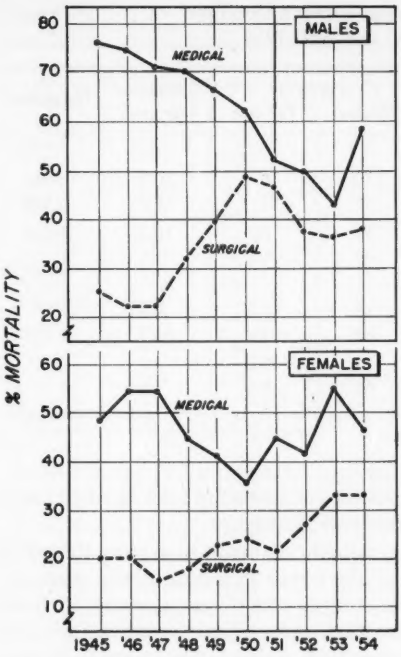

FIG. IV. *Combined five-year mortality rates, according to sex, with three-year smoothing, of patients in Smithwick groups* III *and* IV.

the cases—5 out of 6—were in group II. A precipitous fall in mortality of medically treated men is seen in 1950. There is also a trend toward higher mortality in the surgical patients. In the women, the downward trend among medically treated patients is more gradual and the increase among surgically treated patients is very slight.

The patients in groups III and IV (see figure IV) comprise 28 per cent of the surgical cases and 29 per cent of the medical cases. The numbers are, therefore, less than in groups I and II and may be responsible for the more erratic swings in mortality rates. There were 84 per cent in group III. Again, in the men, a steep downward trend in mortality of medically treated patients—from about 75 to about 50 per cent—was observed, while the mortality in the surgically treated cases rose from about 25 to about 40 per cent. A surprising lack of change is seen in the female patients. Here the mortality has remained at between 40 and 50 per cent in medically treated patients and 20 to 30 per cent in surgically treated patients. Some trend toward an increase in mortality rate in the surgically treated patients is seen but is not statistically significant.

A summary of the above material which has been presented in trend curves, is shown in table 4 and in bar graph form in figure V. The mortality rates in the period 1944-49 are compared with mortality rates in the period 1950-54. It will be noted that the mortality rate improved in the medically treated patients of all groups except the women in groups III and IV. There is statistically a highly significant reduction in mortality of the medically treated male patients after 1950. The male surgical patients, on the other hand, show a slight but nonsignificant rise in mortality from 1950 to 1954, or from the early to the late period. The female medical patients in groups I and II show a significant decrease in mortality, but the female surgical groups show a slight and insignificant rise in mortality. The male medical patients in groups III and IV show a statistically significant drop in mortality. The male surgical patients in these groups, on the other hand, show a statistically significant rise in mortality in five years. However, the mortality rates for the surgically treated patients for both periods are consistently lower than those for the medically treated group. Female patients in groups III and IV show no significant change whether treated medically or surgically. It is of interest that the mortality rate of the surgically treated

TABLE 4 **Chi-Square Tests of Significance Between Five-Year Mortality Rates for 1944-1949 and 1950-1954**

Type of treatment	Group	1944-1949 Number	1944-1949 Per cent	1950-1954 Number	1950-1954 Per cent	Differential (Per cent)	Chi-square
Medical							
Men	I & II	260	37.3	120	16.7	20.6	15.46*
	III & IV	154	73.4	60	55	18.4	5.09†
Women	I & II	291	21.3	131	10.7	10.6	6.10†
	III & IV	73	46.6	44	45.5	1.1	1
Surgical							
Men	I & II	413	14.5	128	21.1	6.6	2.65
	III & IV	179	28.5	88	43.2	14.7	5.09†
Women	I & II	526	7.8	122	9.8	2	1
	III & IV	145	19.3	41	26.8	7.5	1

*p=0.01
†p=0.05

patients, even after 1950, is lower than that of the medically treated patients.

The possibility that age differences could be responsible for results was explored by examining the same data but excluding all patients over 50. This exclusion did not significantly change the patterns of mortality rates in any group, however (figure VI).

A further attempt to explore the cause for the trends in mortality was made by examining the causes of death in both medical and surgical groups before and after 1950 (table 5). We have had some evidence indicating that sudden death may be precipitated in certain severely ill cardiac patients by the use of the chlorothiazide drugs, especially in patients who were taking digitalis without potassium supplement. This possibility does not seem to be a real factor in increasing the mortality rate in this group of patients, because the cardiac deaths in the late period were no greater than in the early period.

We have also suspected that cerebrovascular accidents may be caused by acute postural hypotension, which may be brought about in some instances by the use of some of the newer antihyper-

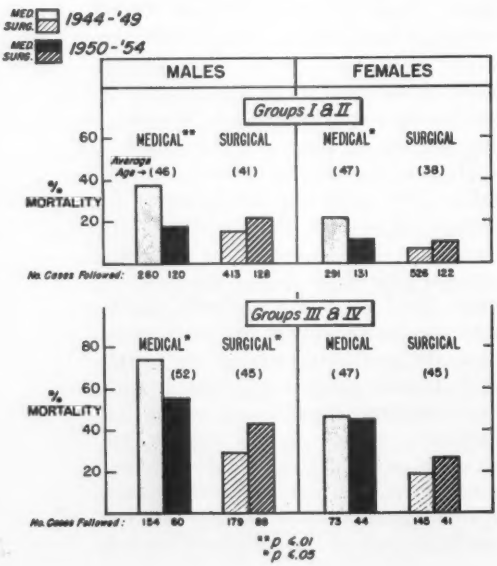

FIG. V. *Five-year mortality rate averages of 2,775 patients treated medically or surgically before and after 1950 (see key). (Top) Combined groups* I *and* II *according to sex and form of treatment. (Bottom) Combined groups* III *and* IV *according to sex and form of treatment.*

TABLE 5 **Causes of Death Based on Five-Year Mortality Rates**

Type of treatment & group	Years	Cases	Per cent total mortality	Per cent brain	Per cent heart	Per cent kidney	Per cent unrelated	Per cent cause unknown	Per cent operative*
Medical									
I & II	1944-1949	551	25.40	11.25	7.80	3.99	1.45	0.90	
III & IV	1944-1949	230	63.91	29.13	20	7.82	1.30	5.65	
I & II	1950-1954	251	11.95	3.98	4.78	0.40	1.19	1.59	
III & IV	1950-1954	104	41.34	13.46	19.23	7.69	0	0.96	
Surgical	1944-								
I & II	1949	939	11.07	3.83	3.51	0.85	1.81	0	1.06
III & IV	1944-1949	324	25.92	11.72	5.86	2.16	1.85	1.54	2.77
I & II	1950-1954	250	14.80	5.60	4	1.20	1.60	0.40	2
III & IV	1950-1954	129	28.68	8.52	6.97	4.65	0.77	0.77	6.97

*Operative mortality is based on 96 per cent of the total groups of patients, since 4 per cent were not traced and therefore omitted from this study.

tensive drugs. This might be especially true if the patient has had surgical treatment before drug therapy. Here again, this does not seem to be the case in the patients of this study.

It is interesting that kidney failure accounted for fewer deaths in each group of surgically treated patients than in the corresponding medical group except for patients in medical groups I and II who were studied from 1950 to 1954.

Conclusions

The hypertensive patients treated medically after 1950 had a statistically significant decrease in five-year mortality rates with the exception of the female patients in groups III and IV. This cannot be explained on the basis of difference in composition of the population under comparison as regards age, sex, or severity of cardiovascular disease. The reason for the decrease in mortality of medically treated cases since 1950 may be either some unrecognized factor or the introduction of newer antihypertensive drugs. We believe that the latter is the case.

Since details as to the form and inten-

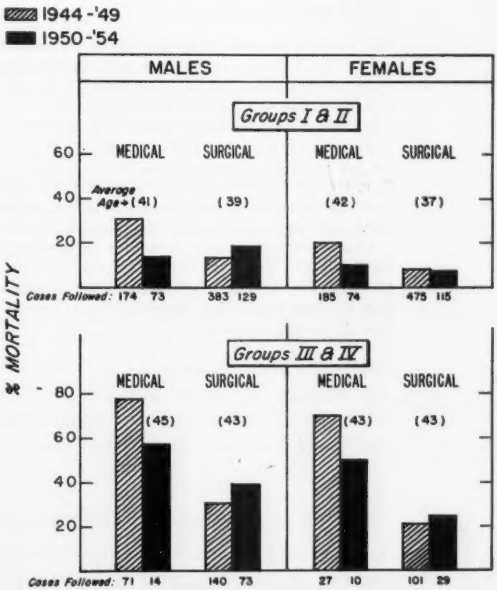

FIG. VI. *Five-year mortality rate averages of patients 50 years of age and under treated medically or surgically before and after 1950 (see key). (Top) Combined groups* I *and* II *according to sex and form of treatment. (Bottom) Combined groups* III *and* IV *according to sex and form of treatment.*

siveness of the medical treatment for 80 per cent of the patients are lacking, no definite conclusions can be drawn. The observations point to the need for a more refined study, and this is currently being made. The results also suggest an upward trend in the five-year mortality rates in surgically treated groups. However, this trend is statistically significant only in the male patients in groups III and IV. The rate in the surgically treated group is still lower than in the medically treated group.

The factor of chance in the selection of treatment must be considered. There is a possibility that the patients after 1950 who responded easily to medical treatment were not referred to the surgeons, while those patients who did not respond to medical therapy were more apt to be referred for surgical treatment. There is, therefore, the possibility that good-risk and more responsive patients have shifted since 1950, with the advent of better drugs, from the surgical to the medical side.

We wish to thank Dr. Reginald H. Smithwick for giving us full access to his patients' records. Without his foresight in systematic tabulation and recording of data on these patients in the past, this study would not have been possible.

We also wish to thank Dr. Robert W. Wilkins for his helpful suggestions and Dr. Raymond J. Walther for his help in compiling this information. Mr. John E. Alman, Boston University, advised and assisted us with the statistical data.

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Dietary cholesterol and the pathogenesis of atherosclerosis

WILLIAM E. CONNOR, M.D.
IOWA CITY

Recent human and animal studies have emphasized the important role of dietary cholesterol in the pathogenesis of hypercholesteremia, atherosclerosis, and ultimate myocardial infarction. Thus cholesterol content as well as fat content should be controlled in therapeutic or prophylactic diets.

WILLIAM E. CONNOR *is with the Cardiovascular Research Laboratories, Department of Internal Medicine, State University of Iowa College of Medicine.*

Current approaches to the treatment and prevention of coronary atherosclerosis have been centered on the effects of dietary fat upon the serum cholesterol concentration. The substitution of the largely polyunsaturated vegetable oils for saturated animal fats in the American diet has almost always produced lowering of the serum cholesterol. This change in serum lipids has been taken to indicate a beneficial effect upon human atherosclerotic disease, although there are not as yet conclusive clinical studies to document this point.

Recent reviews of the role of diet in human atherosclerosis have in general ignored or refuted the idea that dietary cholesterol is an important factor. Indeed, the emphasis has been placed upon dietary fat, as a recent statement of the American Heart Association clearly indicates.[1] Thus many, but not all,[2] therapeutic diets are defined in terms of their fat content without mention of dietary cholesterol. This paper will suggest that, in addition to dietary fat and other factors, dietary cholesterol is an important consideration in the pathogenesis of hypercholesteremia and atherosclerosis. Evidence bearing on this problem will be derived from 3 sources: experimentally induced atherosclerosis in animals, epidemiologic studies in different populations, and recently reported metabolic studies in man.

Experimental atherosclerosis in animals

Cholesterol is almost always an essential component of diets designed to produce

hypercholesteremia and atherosclerosis in animals. In 1912, Anitschkow elucidated the pathogenesis of atherosclerosis in rabbits. Ignatowski and Saltykow had previously noted that atheroma resulted when rabbits were given a diet rich in such animal foods as eggs, milk, and meat. Anitschkow discovered that the pathogenic constituent of these foods was cholesterol, because when he fed rabbits 0.5 per cent cholesterol dissolved in sunflower seed oil, prompt hyperlipemia and, ultimately, the characteristic lesions of the aorta and coronary arteries developed.[3]

Subsequent investigators found that the feeding of the cholesterol-vegetable oil mixture or foods rich in cholesterol and fat induced hypercholesteremia and atherosclerosis in many other species, including the guinea pig, chicken, rat, hypothyroid dog, pig, and monkey.[4] Extensive coronary atherosclerosis and myocardial infarction have been produced in the monkey by the long-term feeding of a diet rich in cholesterol and butterfat.[5] Myasnikov and associates[6] induced myocardial infarction in cholesterol-fed rabbits simultaneously stressed in various ways. The feeding of cholesterol over a period of time set the stage for infarction to be produced later. Thus, in animals, the underlying dietary factors in the pathogenesis of coronary atherosclerosis and ultimate ischemic heart disease could be formulated as follows:

Dietary cholesterol and fat→hypercholesteremia→early atherosclerosis→ occlusive atherosclerosis→myocardial infarction.

Abnormal quantities of both cholesterol and fat in the diet apparently provide a maximal atherogenic effect. Figure I illustrates that, in rabbits fed large quantities of a hydrogenated vegetable shortening for nine months, hypercholesteremia or atherosclerosis did not develop. The addition of cholesterol to the diet led to a prompt elevation of the serum cholesterol and the ultimate development of atheroma. Rabbits fed a combination of corn oil and cholesterol were not protected despite the presence of a large quantity of polyunsaturated fat in the diet.[7] Others have reported similar findings with diets containing lesser quantities of fat.[4] Since the time of Anitschkow, the usual diet for the production of experimental atherosclerosis has been cholesterol plus a liquid vegetable oil with a high content of polyunsaturated fat.[8]

Epidemiology of atherosclerosis

The incidence of coronary heart disease is very low in population groups which

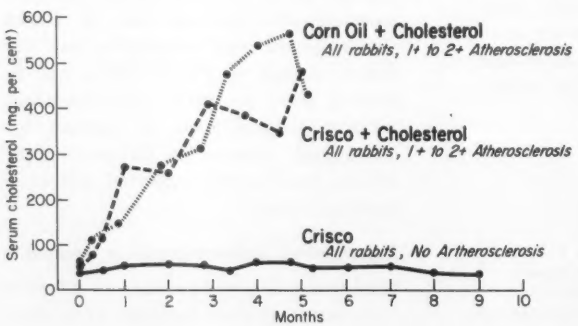

FIG. 1. *Response of rabbits to dietary cholesterol and fat. Each group of rabbits was fed a different diet: 18 per cent Crisco, 18 per cent Crisco plus 0.25 per cent cholesterol, and 18 per cent corn oil plus 0.25 per cent cholesterol. Aortas were examined for atherosclerosis and graded 1 to 4+. Fat, supplied at the 18 per cent level, made up 40 per cent of the total calories.*

consume diets low in total fat, saturated fat, cholesterol, and animal protein.[4] These diets contain a low percentage of total calories from foods derived from animal sources and have a large quantity of carbohydrates in the form of cereals, fruits, roots, and other vegetables. Extensive clinical and autopsy studies have confirmed the data derived from death rate statistics, namely, that people who eat this kind of a diet have little coronary artery disease and indeed less atherosclerosis generally. These include highly industrialized populations, such as the Japanese, as well as many groups with other cultures, such as the Guatemalans and Africans. As a rule, the adults of these populations have low serum cholesterol concentrations, which range from 140 to 170 mg. per cent.

On the other hand, populations which eat the high-fat, high-saturated-fat, high-cholesterol diet consumed in the United States have a high incidence of coronary heart disease, which tends to be similar to the incidence in the American population. This group includes the British, Canadians, and Australians, as well as many of the peoples in Western Europe. Jolliffe and Archer[9] obtained excellent statistical correlation between the death rates from coronary heart disease and the dietary intakes of saturated fat and animal protein, whereas the data of Yerushalmy and Hilleboe[10] gave stress to calories derived from animal fat and protein.

Since most of the commonly consumed saturated fats are derived from animal sources, and since the usual sources of animal fats and animal protein contain appreciable amounts of cholesterol, it is clear that a close relationship probably exists between dietary cholesterol and coronary heart disease. Such a relationship has been drawn in detail for 24 different countries (figure II). The selection of the countries was made on the basis of available information. All countries with both mortality statistics for men aged 55 to 59[11] and food supply data[12] were included. The average daily cholesterol intake per inhabitant was computed from the quantities of various dietary items which contain cholesterol.

There was an excellent correlation between the cholesterol intake and the mortality from coronary heart disease. The coefficient of correlation was 0.8281. For example, the United States had the highest mortality rate—732 per 100,000—and also the highest average daily cholesterol intake—584 mg. Japan, Portugal, Greece, Ceylon, Yugoslavia, and Formosa had one-sixth or one-seventh lower mortality than the United States and also much lower cholesterol intakes—from 62 to 143 mg. per day.

It is well known that the serum cholesterol levels of populations with a high incidence of coronary heart disease are elevated—220 to 260 mg. per cent—compared with levels found in the Japanese and other populations with a low incidence of coronary heart disease. Thus the same train of events that implicate diet in the multifactorial etiology of coronary heart disease can be listed from the epidemiologic data as was deduced from the evidence in experimental animals: namely, that

High intakes of dietary cholesterol and fat (especially saturated fat)→hypercholesteremia→coronary heart disease.

The opposite relationship also appears valid:

Low intakes of cholesterol and fat in the diet→low serum cholesterol→low incidence of coronary heart disease.

Thus a diet that does not predispose to hypercholesteremia and coronary heart disease might have the following requirements: dietary cholesterol below

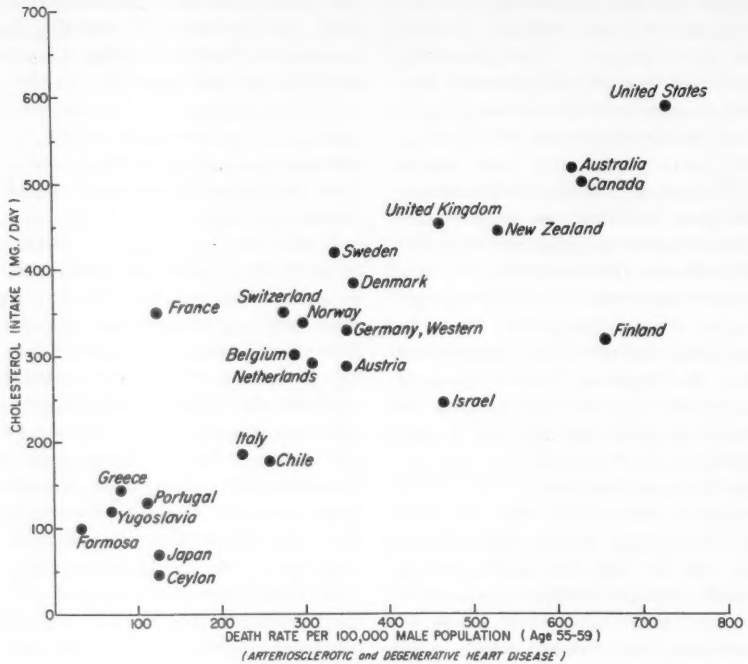

FIG. 11. *Death rate from arteriosclerotic and degenerative heart disease (category B26) compared with daily intake of cholesterol in diet for 24 countries. Death rate is expressed in deaths per 100,000 population for men aged 55 to 59, 1955 to 1956.*[11] *Cholesterol intake in milligrams per day was computed from food balance sheets for years 1952 through 1956.*[12] *The coefficient of correlation (r) was 0.8281 and was highly significant.*

150 mg. per day, saturated fat below 10 to 15 per cent of total calories, and total fat no higher than 20 to 25 per cent of the total calories.

In presenting the key role of diet in the pathogenesis of atherosclerosis, I do not mean to imply that diet is the sole contribution to the clinical consequences of this disease. Heredity, life stresses, lack of exercise, hypercoagulability of blood, altered hormonal secretions, and other disease states such as diabetes, hypertension, and nephrosis are also contributing factors.

Extremely interesting is the fact that countries with a low mortality rate from coronary artery disease do not have an especially high intake of unsaturated or polyunsaturated fat. Again from the data of Jolliffe and Archer,[9] Japan, Yugoslavia, and Ceylon had very low death rates from coronary heart disease; their unsaturated fat intakes were 6.5, 5.9, and 3.4 per cent of the total calories, respectively. The unsaturated fat intake in the United States was 5.7 per cent of the total calories and in the United Kingdom, 3.4 per cent of total calories. Thus the people of countries with low and with high death rates from coronary heart disease had similar intakes of unsaturated fat. Epidemiologic evi-

dence does not support the idea that Americans should greatly increase their intake of unsaturated fat.

Effect of dietary cholesterol upon serum cholesterol in man

Cholesterol consumed in the human diet is usually believed to have little effect upon serum cholesterol levels. Consequently, recommendations about therapeutic diets for the treatment of hypercholesteremia and atherosclerosis either avoid any direct consideration of dietary cholesterol or indicate why it need not be restricted in the diet of man. There are several reasons for these opinions. Keys and associates[13] found that the feeding of cholesterol to men receiving an almost fat-free diet failed to induce increases in serum cholesterol levels. Since the absorption of cholesterol from the intestinal tract is dependent in part upon the presence of fat, this result is not surprising. In another study, the serum cholesterol concentrations did not change when crystalline cholesterol was added to diets already containing considerable amounts of cholesterol. It is now known that once a certain intake level of dietary cholesterol is reached, further increments have little effect.[14, 15]

Also, it has been reasoned that, if cholesterol in the diet were reduced, the liver would compensate by synthesizing more cholesterol from acetate, a metabolic building block readily available from carbohydrate or protein. After this adjustment, the net effect upon the serum cholesterol would be minimal.[1] This line of reasoning is open to criticism on both logical and factual grounds.[2]

Recent evidence suggests, on the contrary, that dietary cholesterol does in fact greatly alter the serum cholesterol concentration in man. During the past three years, 5 separate experimental studies carried out by 3 different groups bear particularly upon this question. Two approaches have been used: Subjects have been fed (1) a fat-free diet followed by a diet containing fat and variable amounts of cholesterol or (2) a diet constant in the amount of fat and fatty acid composition followed by addition or subtraction of cholesterol from the diet. In this latter kind of study, only one variable is changed.

Beveridge and associates[16] fed their subjects a fat- and cholesterol-free diet for eight days and then added to the diet for another sixteen days a butterfat fraction, itself virtually cholesterol-free. Fat then comprised 30 per cent of the total calories. As might be expected, the addition of this butterfat fraction—a fat largely saturated—produced a rise in the serum cholesterol. The use of another butterfat fraction containing cholesterol—1,290 mg. per 950 calories—caused further increases in serum cholesterol levels. In a second study,[14] crystalline cholesterol in gradually increased amounts was added to the diet during the period of butterfat feeding. When 634 mg. or more cholesterol was given, the increments in serum cholesterol were greater than the increment resulting when only the cholesterol-free butterfat fraction was added to the previously fat-free diet—that is, an increase of 25 mg. per cent with the butterfat fraction alone and an increase of 42 mg. per cent with butterfat plus cholesterol. Bronte-Stewart[17] has reported a similar type of study. A fat-free, and presumably cholesterol-free, feeding period was followed by the addition of whole egg yolk and various egg yolk fractions. The serum cholesterol levels in his subjects increased greatly only when both the cholesterol and triglyceride fractions of egg yolk were fed together.

Summarized in the table are 2 other studies which, maintaining a constant fat intake, have shown definite effects of dietary cholesterol upon serum cholesterol and phospholipid. Both utilized a basic diet containing 40 per cent of the total calories as fat and having an iodine number of about 85 and a fatty acid composition of about 34 per cent saturated fat, 40 per cent monounsaturated fat, and 26 per cent polyunsaturated fat. Egg yolk was incorporated into the diet in such a way that none of these basic parameters of the diet was altered. Only the cholesterol content was changed.

In the 1959 study,[18] 3 men previously receiving a general diet were given a cholesterol-free diet and had an average serum cholesterol decrement of 61 mg. per cent; 3 other men given from 1,650 to 4,800 mg. cholesterol had an average serum cholesterol increase of 30 mg. per cent. These changes were sustained for the eleven weeks of study. Then, in a switchback procedure but using diets of mixed natural foods, cholesterol was removed from the diets of those men previously receiving cholesterol, and the serum cholesterol fell 102 mg. per cent. Simultaneously, cholesterol was added to the cholesterol-free diets of the other men, and the serum cholesterol rose 57 mg. per cent.

In the 1960 study,[15] it was found that the presence or absence of as little as 475 mg. of dietary cholesterol in the form of egg yolk (equivalent to 2 egg yolks per day) had a great effect upon the serum cholesterol. Quantities of cholesterol in the diet from 475 to 1,425 mg. produced similar effects. Crystalline cholesterol also caused significant increases in serum cholesterol concentrations. These results were noted during 4 dietary periods of three weeks each which alternated between cholesterol-free and cholesterol-containing diets. In both studies, the serum phospholipid changed in the same way as did the serum cholesterol in response to the changes in dietary cholesterol. The changes noted occurred with both formula-type diets and diets composed of mixed natural foods. Thus, the serum cholesterol concentrations of both man and experimental animals are affected by cholesterol in the diet.

TABLE **Effect of Dietary Cholesterol Upon Serum Lipids**
(Summary of 2 Studies)

	Number of subjects	Control dietary period: Kind of diet*	Iodine no.	Cholesterol content (mg.)	Length (wks.)	Exp: Kind of diet*
1959 Study[18]	3	General diet	66	900	5	mula
	3	General diet	66	900	5	mula
	3	Formula	85	1,650-4,800†	11	ixed tural ods
	3	Formula	85	0	11	ixed tural ods
1960 Study[15]	6	Formula	85	0	3	mula
	6	Formula	85	475-1,425†	3	mula
	6	Formula	85	9	3	mula

* Amount of fat for all diets was 40 per cent of the total calories. Fatty acid composition for all diets with an iodine number of 85 was saturated, 33 to 34; monounsaturated, 41; polyunsaturated, 25 to 28 per cent.

† Cholesterol supplied in the form of egg yolk.

‡ Cholesterol given as crystalline cholesterol.

Atherosclerosis and hepatic synthesis of cholesterol

As mentioned earlier, dietary cholesterol has not generally been considered an important influence upon the serum cholesterol level, and thus upon atherosclerosis, because of the well-known reciprocal relationship between cholesterol in the diet and hepatic synthesis from acetate. This postulation must be examined in the light of additional observations. First, contrary to the results in animal experiments, large

Experimental dietary period				Change in serum lipids	
Iodine no.	Cholesterol content (mg.)	Length (wks.)	Cholesterol	Phospholipid	
			(mg. per cent)		
85	1,650-4,800†	11	+30	+21	
85	0	11	−61	−38	
85	0	3	−102	−49	
85	2,400†	3	+57	+39	
85	475-1,425†	3	+69	+42	
85	0	3	−55	−44	
85	1,200-3,600‡	3	+19	+22	

amounts of dietary cholesterol have not been shown to suppress greatly the hepatic synthesis of cholesterol in man.[19] This means that cholesterol absorbed from the diet is probably an added increment to the amount of cholesterol synthesized by the liver.

Secondly, dietary cholesterol is always transported in the blood in the form of that large lipoprotein aggregate known as the chylomicron. Cholesterol synthesized by the liver is usually carried in much smaller lipoproteins. It is of interest that, in biliary cirrhosis, the phenomenally high serum cholesterol concentration, at times over 1,000 mg. per cent, probably results from augmented hepatic synthesis.[20] Despite the lipid abnormality, greatly accelerated atherosclerosis has not been reported.[21] Sera from these patients are clear and do not contain great quantities of chylomicrons.

Furthermore, atherosclerosis in animals rarely is caused by an abnormally high rate of cholesterol synthesis by the liver. Dietary cholesterol and fat, not cholesterol of direct hepatic origin, usually lead to this disease in animals. Thus attempts to treat hypercholesteremia by blockage of hepatic synthesis, as with triparanol (MER/29), would not seem to be aimed at the basic problem, which would remain as long as the ingestion of dietary cholesterol and fat was continued. Exaggerated hepatic synthesis of cholesterol has not been demonstrated for the vast majority of patients with hypercholesteremia and atherosclerosis.

Acute changes in serum lipids; chylomicronemia

The serum lipid changes resulting from the chronic ingestion of cholesterol and fat in the diet are commonly described in terms of cholesterol, phospholipid, and triglyceride measured in the fasting state. Acute changes in the serum lipoproteins occur after the absorption of cholesterol and fat from the gastrointestinal tract. The chylomicron is the lipoprotein fraction that initially transports this exogenous lipid, first in the thoracic duct lymph and then in the blood. After a lipid-rich meal, chylomicronemia is present for many hours and imparts lactescence to the plasma. Chylomicrons are large particles, up to 1 μ in size, and circulate as a colloidal suspension rather than in solution.

Noting these characteristics, Moreton[22] suggested that chylomicrons might be important in the pathogenesis of atherosclerosis. Patients with idiopathic hyperlipemia have marked chylomicronemia twenty-four hours of the day and are prone to develop premature coronary atherosclerosis.[23] Animals used in the experimental production of atherosclerosis also have chylomicronemia. This disorder may be observed in the rat but is especially notable in the rabbit a few hours after the first cholesterol-rich meal and remains permanently estab-

lished for as many months as the cholesterol feeding is continued.

Chylomicrons pass through the endothelium of capillaries. As Hueper[24] has illustrated for other colloidal particles, perhaps chylomicrons are the lipoprotein particles which infiltrate the arterial intima to set up the atheromatous deposit. If so, then dietary cholesterol and fat may be important in the pathogenesis of atherosclerosis because of the chylomicronemia which their absorption initiates. Less chylomicronemia would result from the consumption of diets low in cholesterol and fat.

Dietary treatment of hypercholesteremia and atherosclerosis

If the evidence from all avenues of inquiry—animal experiments, epidemiologic studies in different population groups, and metabolic studies in human beings—is considered, a diet possibly suitable for the treatment and prevention of atherosclerotic disease in man may be suggested. As has already been indicated, such a diet should probably be low in cholesterol, total fat, and saturated fat and relatively high in carbohydrate content, from cereals, fruits, and vegetables. Its fat content should consist largely of mono- and polyunsaturated fatty acids. The caloric content may be adjusted to individual needs to maintain or achieve ideal body weight. The characteristics of such a diet have been tentatively advanced: 100 mg. or less of cholesterol; 20 per cent of the total calories as fat; an iodine number of about 85; and a fatty acid composition of about 25 per cent saturated, 43 per cent monounsaturated, and 27 per cent polyunsaturated. A protein content of 75 gm. is ample—41 gm. from skim milk, lean meat, poultry, and fish and 34 gm. from cereals and other vegetable sources. This diet contains all essential nutrients. Its use would, theoretically at least, avoid extensive chylomicronemia. When consumed in place of the usual American diet, a 15 to 20 per cent lowering of the serum cholesterol level may be achieved.[25]

Summary and conclusions

Recent evidence about the role of dietary cholesterol in the pathogenesis of hypercholesteremia and atherosclerosis has been reviewed. Cholesterol in the diets of experimental animals is an important cause in the development of high serum cholesterol concentrations, atheroma formation, and ultimate myocardial infarction. A review of the epidemiology of coronary heart disease in different human population groups indicates a significant relationship between the amount of cholesterol consumed in the diet and the mortality from coronary heart disease. Five separate dietary studies in men have suggested that, contrary to previous impressions, dietary cholesterol significantly affects the serum cholesterol concentrations in human beings.

These lines of investigation indicate that the role of dietary cholesterol in human atherosclerotic disease should be reconsidered. This view would not in any way contradict the well-established idea that the amount and kind of fat in the diet are of great significance in hypercholesteremia and atherosclerosis. To be emphasized again is that these are multifaceted problems. Dietary cholesterol is but one important component. Diets used to treat or prevent human hypercholesteremia should therefore be designed in terms of the cholesterol content as well as of the fat content.

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ENERGETIC TREATMENT of pathologic fractures is desirable, since life expectancy is short. A combination of surgical internal fixation and radiotherapy should be used.

To secure fractures of the femoral neck or intertrochanteric region of the femur, a Smith-Petersen or Jewett nail is used, or a replacement arthroplasty is performed. An intramedullary nail should be used for fractures of the middle third of the femur or humerus. The shaft should be exposed and the nail passed with direct vision to prevent false passages. To help assess radiotherapy, a biopsy should be taken at the fracture site.

Radiation is begun early. For undifferentiated tumors, approximately 3,000 r should be delivered through multiple ports in two weeks. If the fixation device is used, the entire long bone is irradiated as tumor cells may be forced down the medullary canal by the nail.

O. R. ROTH: Supervoltage radiotherapy and intramedullary fixation in the management of pathological fractures of long bones. Maryland State M. J. 9: 310-311, 1960.

Side effects of nicotinic acid in treatment of hypercholesteremia

KENNETH G. BERGE, M.D.
ROCHESTER, MINNESOTA

Nicotinic acid in large oral doses has proved very effective in lowering elevated levels of cholesterol in the blood. However, side effects limiting the general usefulness of this treatment include gastrointestinal irritation, hepatic dysfunction, jaundice, abnormalities of glucose tolerance, and hyperuricemia.

KENNETH G. BERGE *is on the staff of the Section of Medicine, Mayo Clinic and Mayo Foundation, Rochester.*

Clinical data, animal experimentation, and epidemiologic studies have indicated a causal relationship between elevated levels of cholesterol in the blood and atherosclerosis.[1] Although there is still no definite evidence that correcting hypercholesteremia retards atherogenesis or causes regression of established atheromatous lesions in man, there is much interest in treating persons who have increased blood cholesterol, especially when the increase is associated with a personal or family history of vascular disease developing at an early age.[2] Indeed, the long-term observation of patients in whom the hypercholesteremia has been corrected by an effective regimen and the comparison of these patients with untreated hypercholesteremic patients may ultimately settle whether or not such treatment is beneficial.

In spite of extensive studies of a variety of approaches to the treatment of hypercholesteremia, the ideal agent or dietary regimen has yet to be found. Inadequate effectiveness, prohibitive expense, impracticality, side effects, and possible toxicity are some of the problems shared by all of the currently available therapeutic programs. However, several agents have been sufficiently effective in altering hypercholestere-

mia to warrant continued use on an investigational basis in selected patients. One such agent has been nicotinic acid given in large doses of 1.5 to 6 gm. daily. Such use of nicotinic acid has been studied in an investigational series at the Mayo Clinic since 1955.[3] Without alteration in type or content of dietary fat, a mean decrease in the level of plasma cholesterol of 17 per cent of pretreatment values occurred during the first three months of treatment with 3.0 gm. given daily. Furthermore, 80 per cent of 51 patients with hypercholesteremia (mean level of plasma cholesterol, 327 mg. per 100 cc.) treated for a year or longer had a mean level of cholesterol of less than 250 mg. per 100 cc. for at least three months on the optimal dosage. Results reported by others also indicate that nicotinic acid in large doses is one of the most consistently effective of the agents currently used in treatment of familial or idiopathic hypercholesteremia.[4-8] Although the mechanism of such action of nicotinic acid has been the subject of much interest and investigation, it is still unknown.

Side effects associated with the oral administration of nicotinic acid have been sufficiently frequent to limit or contraindicate its use in some persons and to require careful observation of all patients on this treatment. These untoward effects will be reviewed in this report.

Cutaneous effects

Cutaneous flushing or pruritus is experienced by all patients at the onset of treatment. Although these symptoms are more severe initially than those associated with the more conventional "flushing" dose of nicotinic acid, they usually subside noticeably within a few days after the start of treatment. Only 3 per cent of the patients in our previously mentioned investigational series experienced severe flushing after the initial two weeks of treatment. Although 59 per cent experienced mild flushing indefinitely, it usually was not objectionable and occurred primarily after the first dose of nicotinic acid each day or when the drug was taken without food.

Reassurance that the severe flushing will subside rapidly with continued treatment has usually taken care of this problem, which has not seemed to warrant all of the attention it has received. The use of special preparations of nicotinic acid intended to reduce or eliminate flushing frequently has led to enhancement of other, more troublesome side effects, as will be discussed. Nicotinamide, which does not cause flushing, has no cholesterol-lowering effect.[4]

A less frequent cutaneous effect has been dryness and pruritus of the skin, resembling asteatosis. Parsons and Flinn[4] observed brown pigmentation in the axillae and over pressure points in 2 patients while they were taking large doses of nicotinic acid. These changes subsided completely when nicotinamide was substituted.[4] Ruiter and Meyler[9] reported the occurrence of skin changes resembling ichthyosis vulgaris, in which the color of the skin was described as grayish brown with patchy areas of depigmentation, in one case after treatment with large doses of nicotinic acid. This cleared after withdrawal of treatment. My colleagues and I have observed brownish hyperpigmentation of the arms in 1 case; the condition of the skin returned to normal within two months after use of nicotinic acid was discontinued. The significance and mechanism of these abnormalities are unknown.

Gastrointestinal symptoms

Approximately one-fifth of the patients in our series experienced symptoms of gastrointestinal irritation with anorexia,

nausea, vomiting, or diarrhea at some time while taking plain nicotinic acid. These symptoms were minimized by the ingestion of nicotinic acid in divided doses with meals and were usually transitory. However, 4 patients discontinued treatment early in the course because of them. Esophagitis developed in 1 patient with a diaphragmatic hernia but cleared up when the dosage of nicotinic acid was decreased.

Some patients who had taken large doses of nicotinic acid for as long as three years subsequently had gastrointestinal symptoms that necessitated either decrease in dosage or withdrawal of the medication. In some, these symptoms were associated with further decrease in the level of plasma cholesterol below the earlier, adequately maintained reduction.

The development or reactivation of peptic ulcer was not observed in our series. Belle and Halpern[5] and Parsons[10] have reported the occurrence or reactivation of peptic ulcer during treatment of hypercholesteremia with large doses of nicotinic acid. Parsons attributed this to the acidity of the drug and reported that buffered nicotinic acid eliminated the symptoms and allowed continuation of treatment in most patients. Altschul and Hoffer[11] had demonstrated earlier that nicotinic acid buffered with sodium bicarbonate was as effective as plain nicotinic acid in decreasing serum cholesterol. We have had no experience with such preparations of nicotinic acid.

Hepatic functional impairment

Twenty-three of 52 patients in the previously mentioned[3] series exhibited at least 1 abnormal result in a test of hepatic function during some period of their treatment with large doses of nicotinic acid (table 1). The abnormalities most commonly observed were cephalin-cholesterol flocculation, grade 3 or 4; mild increases of serum glutamic-oxalacetic transaminase activity; slight increases of serum alkaline phosphatase; and retention of sulfobromophthalein (usually less than 22 per cent in one hour). In 7 instances, the abnormal results of the tests reverted to normal without stopping of treatment with nicotinic acid. In only 3 cases were the abnormalities persistent, but treatment has been continued in this group. Hepatomegaly, splenomegaly, spider nevi, or other physical findings suggesting hepatic disease were not observed.

Jaundice occurred in 2 cases in our series during treatment with nicotinic acid in a sustained-action preparation. In neither case was there a history of exposure to hepatitis. The value for direct-reacting serum bilirubin, which reached a maximum of 2.9 mg. per 100 cc. in 1 case and 5.1 in the other, returned to normal in twenty and twenty-seven days respectively after use of the

Table 1 Tests of Liver Function During Treatment of Hypercholesteremia with Nicotinic Acid

Follow-up of abnormal results		Cases
Returned to normal		12
Without alteration of treatment	5	
With decrease in dosage	2	
When drug was discontinued	5	
Abnormal only during use of placebo or after treatment was discontinued (2 with associated alcoholism)		3
Not rechecked		5
Persistently abnormal with continued treatment		3
Cephalin-cholesterol flocculation	1	
Cephalin-cholesterol flocculation and sulfobromophthalein retention	1	
Cephalin-cholesterol flocculation, sulfobromophthalein retention and alkaline phosphatase	1	
Total cases		**23**

drug was stopped. The results of all other tests of hepatic function also became normal after withdrawal of nicotinic acid. Although the histologic picture in 1 patient who had a needle biopsy of the liver was quite similar to that seen in viral hepatitis, the drug must be accepted as the most likely cause of the jaundice. Studies of hepatic tissue at necropsy in 4 patients who died of coronary disease during treatment with nicotinic acid revealed mild fatty changes in 2 and small focal areas of necrosis of hepatic cells in another.

Other instances of possible hepatotoxic effects of nicotinic acid have appeared in the literature. In the case reported by Rivin,[8] jaundice developed after fourteen months of treatment with large doses of nicotinic acid. The value for serum bilirubin in this patient returned to normal within twenty days after withdrawal of nicotinic acid. Parsons and Flinn[4] noted no abnormalities either in tests of hepatic function or in histologic sections obtained by needle biopsy of the liver in 17 patients after one year of treatment. Subsequently, Parsons[12] has reported increased retention of sulfobromophthalein in 6 of 49 patients after one to three years of treatment. Pardue[13] reported the occurrence of hypoalbuminemia, edema, and abnormal results with tests of hepatic function including a slight increase of serum bilirubin (1.3 mg. per 100 cc.) in 1 patient following treatment with 3 gm. of nicotinic acid given daily for six months. The abnormalities cleared up or largely subsided after withdrawal of the drug.

The cases of jaundice and the case of hypoalbuminemia with edema indicate that the less striking abnormalities in tests of hepatic function that have been observed in other cases during treatment with nicotinic acid warrant careful observation, if not cessation of treatment.

Abnormalities of carbohydrate metabolism

Fasting hyperglycemia was observed in 21 of our 30 cases[3] in which blood sugar was determined while large doses of nicotinic acid were being taken. The increase of fasting blood sugar was usually small, the value for "true" blood sugar being 91 to 110 mg. per 100 cc. However, the results of oral tests of glucose tolerance, done on 27 persons during treatment with nicotinic acid, simulated those in diabetes mellitus in 14, were equivocal in 5, and were normal in 8. In 13 of the 19 patients with abnormal or equivocal results, the results became normal after treatment was stopped, usually within three weeks (table 2). Of 5 other patients who were rechecked after treatment with nicotinic acid was discontinued, 4 gave equivocal results with the glucose-tolerance test for as long as four months, and another had evidence of mild diabetes mellitus six months later. One patient has not been rechecked.

Gurian and Adlersberg[7] were the first to call attention to abnormalities in carbohydrate metabolism during treatment

Table 2 **Effect of Discontinuing Nicotinic Acid on Equivocal or Abnormal Tests of Glucose Tolerance**

Glucose tolerance test	Patients No.	Patients %	Remarks
Remained abnormal or equivocal	5	28	Definite diabetes in 1 patient Equivocal tests after 2, 2½, 3, and 4 months, respectively, in 4 patients
Became negative	13	72	Period for reversal: 2 weeks or less 9 patients 3 weeks 1 patient 2 months 1 patient 3 months 2 patients
Total	18	100	

of hypercholesteremia with large doses of nicotinic acid. They noted hyperglycemia in 5 instances and glucose-tolerance curves simulating those of diabetes mellitus in 2. Belle and Halpern[5] observed an aggravation of diabetes mellitus in 1 case during treatment with nicotinic acid. The significance of these abnormalities in carbohydrate metabolism is not known nor is the underlying mechanism understood. Nevertheless, it would seem reasonable to use nicotinic acid in large doses with great care, if at all, in patients with diabetes mellitus. Certainly one must be well aware of this side effect in order to interpret data pertaining to carbohydrate tolerance in persons so treated.

Hyperuricemia and gout

Levels of serum uric acid of 6.0 mg. per 100 cc. or greater were observed on at least 1 determination in 16 of 26 patients in our series while they were receiving large doses of nicotinic acid. In 8 of these patients, the serum uric acid was increased on all determinations, the mean level being 7.8 mg. Only 2 patients experienced acute gouty arthritis: one had had gout prior to entering the study, and the other has continued treatment for more than two years since the initial single episode without a recurrence. Parsons observed levels of serum uric acid in excess of 6 mg. per 100 cc. in 29 of 40 patients during treatment with nicotinic acid but none had gouty arthritis.[12] The cause of hyperuricemia during such treatment is unknown.

Thyroid function

All patients in our series were euthyroid prior to study and none exhibited signs or symptoms of thyroid dysfunction during treatment with nicotinic acid. Determinations of the basal metabolic rate (B.M.R.) were done during treatment and during the period of placebo administration in four instances. In 2 the basal metabolic rate was decreased during treatment and in the other 2 it was increased. The highest level observed during treatment was +3 per cent and the lowest —12 per cent. Determinations of protein-bound iodine (P.B.I.) were made during treatment in 6 cases and also during the period of placebo administration in 3 of these. In the latter 3 cases, the level of P.B.I. was lower during the period of nicotinic acid treatment and in 1 instance it was 2.9 mcg. per 100 cc. as compared with 5.0 and 5.8 observed during 2 periods of placebo administration.

The level in the 3 cases in which tests were done only during treatment ranged from 3.9 to 7.7 mcg. per 100 cc. In 2 instances, determination of radioiodine uptake by the thyroid gland was measured during treatment and during the period of placebo administration. In one, the twenty-four-hour uptake decreased from 24 to 20 per cent during treatment. In the other case, it increased from 24 to 25 per cent during treatment; this minimal increase was noted at the time that the P.B.I. had decreased to 2.9 mcg. In 1 additional case, the uptake during treatment with 6 gm. of nicotinic acid daily was 26 per cent as compared with 15 per cent following a three-month period of treatment with 4.5 gm. daily. None of the above tests indicated a significant alteration in thyroidal function.

Altschul and Hoffer observed slight increases (6.0 per cent) in the basal metabolic rate of 12 healthy students during treatment with 3 gm. of nicotinic acid given daily for two weeks and this increase persisted for at least one week after treatment was discontinued.[14] They observed that this change was not sufficiently great to suggest a thyroid-like effect of nicotinic acid, however. Belle

and Halpern reported the development of hypothyroidism in one of their cases during treatment with nicotinic acid.[5] The clinical features of myxedema subsided and the low level of serum butanol-extractable iodine returned to normal after treatment with nicotinic acid was discontinued.[15]

Sustained-release preparations of nicotinic acid

In an attempt to overcome the objectionable effects of large doses of plain nicotinic acid, especially the flushing and gastrointestinal irritation, several forms of so-called sustained-action nicotinic acid have been developed. My colleagues and I have studied 3 such preparations in patients who tolerated plain nicotinic acid well:[16] tightly compressed plain nicotinic acid, nicotinic acid combined with a resinous base (Nicospan), and nicotinic acid impregnated into a plastic matrix (Nicotinic Acid Gradumet). Eight of the 9 patients taking the compressed tablet had to discontinue treatment because of side effects. The symptoms experienced, consisting mainly of anorexia, nausea, vomiting, abdominal pain, and malaise, at times resembled those of viral gastroenteritis and even biliary colic. In all cases, the symptoms cleared up promptly when the treatment was stopped. Nine of 14 patients discontinued the use of nicospan and 11 of 17 stopped taking nicotinic acid gradumets because of similar symptoms. Our experience indicates that when a delay in the release of nicotinic acid is achieved, gastrointestinal side effects are greatly accentuated and the cutaneous flushing merely is delayed. Furthermore, as noted earlier in this report, the only jaundice that we have observed during treatment with nicotinic acid occurred during treatment with a delayed-release preparation.

O'Reilly and co-workers[17] studied 1 sustained-release form of nicotinic acid (nicospan) and noted mild flushing in only 3 of 15 subjects after a single dose of 1 gm. Of 10 persons who took 1 gm. 3 times daily for two weeks, 2 had nausea, vomiting, diarrhea and malaise that necessitated discontinuing treatment after seven days and 2 others had nausea throughout the period of treatment. More recently, studies of a salt of nicotinic acid, aluminum nicotinate (Nicalex), have been reported by Parsons.[18] The report included patients observed by others along with 14 of his own. In his own group of 14 patients, 6 experienced severe flushing and three noted gastrointestinal disturbance while taking aluminum nicotinate. He thought that this preparation caused more nausea than did plain nicotinic acid in his own cases, but when the series as a whole was considered, there seemed to be a decreased incidence of gastrointestinal side effects. At this time, no data have been reported to indicate clearly that sustained-release forms of nicotinic acid represent a significant improvement over plain preparations; rather, such preparations have caused increased side effects.

Conclusions

In the continuing search for an effective, practical, and safe means of treating patients with increased cholesterol in the blood, treatment with nicotinic acid in large oral doses has proved to be one of the most effective and practical approaches to date. However, use of this drug has been limited by several side effects. Cutaneous flushing and pruritus are usually severe with only the first few doses. Dryness of the skin and, more rarely, hyperpigmentation may occur with prolonged treatment. Anorexia, nausea, and vomiting or diarrhea may occur either early or late in the course

of treatment, but usually can be minimized by administering the nicotinic acid with food.

Laboratory evidence of hepatic functional impairment has appeared, especially with prolonged treatment, and, in two of our cases as well as in 2 others reported in the literature, jaundice or other signs of hepatic disease developed during medication. Both cases of jaundice in our series occurred with use of a sustained-release preparation of nicotinic acid; this preparation also increased the incidence of the gastrointestinal symptoms noted above. Abnormalities of glucose tolerance simulating those of mild diabetes mellitus have been noted frequently but usually revert to normal after withdrawal of nicotinic acid. Hyperuricemia and, rarely, acute gouty arthritis have also been observed.

Because of these side effects and their possible long-term implications, the use of large doses of nicotinic acid must still be regarded as an investigational treatment for hypercholesteremia.

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Recurrent pulmonary embolism as remediable cause of heart failure

EDWARD A. EDWARDS, M.D.,
LEWIS DEXTER, M.D., and
WILLIAM C. DONAHUE, B.S.
BOSTON

The results of control of recurrent pulmonary embolism were assessed in 26 patients with heart failure. Patients with pre-existing arteriosclerotic heart disease did well; those with pre-existing rheumatic disease did poorly; fair results were achieved when cor pulmonale was due to recurrent embolism alone. Emphasis on anatomic and technical factors in vein ligation may improve results.

EDWARD A. EDWARDS *is senior associate in surgery, Peter Bent Brigham Hospital, and associate clinical professor of anatomy, Harvard Medical School, Boston.* LEWIS DEXTER *is clinical professor of medicine at Harvard Medical School and is physician, Peter Bent Brigham Hospital.* WILLIAM S. DONAHUE *is a third-year student at Harvard Medical School.*

■ In recent years, it has become evident that recurrent pulmonary embolism may constitute a remediable cause of heart disease. Episodes of embolism, recurring over weeks or months, may by themselves produce failure of the right or of both sides of the heart. More frequently, pulmonary embolism may complicate established heart disease and be responsible for episodes of heart failure. In either event, once emboli have recurred over a period of some weeks, spontaneous recovery is not to be expected. Left untreated, the patient's course will be inexorably downhill, with death usually occurring in weeks or months.

Recognition of the problem does not necessarily result in successful management. The diagnosis is often difficult to establish, as the signs of the embolism are most often those of right or left heart failure. Once the diagnosis is made, there often remains a lingering doubt that symptoms may be due to pulmonary artery disease rather than to fresh embolism. If, indeed, the lesion is embolic, the possibility exists that the offending clot may have come from the right side of the heart.

There is little room in this disease for treatment which is short of definitive. The diagnosis often rests on the presence of right heart strain, when, accord-

ing to the findings of Gibbon and associates,[1] at least two-thirds of the pulmonary arterial tree is usually already occluded. In this situation, anticoagulants are usually ineffective, or at least uncertain in effect.

In order to evaluate our ability to recognize and treat this malady, we have analyzed the records of 26 recently observed cases at Peter Bent Brigham Hospital—cases in which (1) embolism had recurred for six weeks or more before definitive treatment was offered and (2) the patients had been followed for two years or more or to demise. Contrary to expectations, we found results of therapy fair in cor pulmonale without antecedent heart disease, good when embolism had complicated arteriosclerotic heart disease, and uniformly disappointing in the presence of rheumatic and some miscellaneous heart conditions. The poor results are due mainly to the pulmonary and cardiac statuses of the patients. Failures may also occur, however, due to anatomic variations in the veins or to technical errors, and these will be discussed.

Material and results

Patients. The 26 cases of cor pulmonale could be divided into 3 groups: 11 with recurrent pulmonary embolism without antecedent heart disease; 6 with embolism complicating arteriosclerotic heart disease; and 9 with complicating rheumatic or miscellaneous varieties of heart disease (table 1), the latter including 1 each of idiopathic cardiac fibrosis, idiopathic cardiac hypertrophy, and Eisenmenger's syndrome. Women predominated slightly in the entire series (16 women, 10 men) and in each group.

Salient clinical features. When embolism alone caused the heart failure, the outstanding symptoms were weakness, progressively increasing dyspnea, chronic cough, and intractable peripheral edema—symptoms similar to those described with primary pulmonary hypertension.[2-5] Precordial chest pain was frequently mentioned and often appeared to be anginal or anginoid.

Symptoms referable to embolism itself, such as syncope, pleural pain, and hemoptysis, were less often mentioned. Hospitalization frequently proved extremely useful, since episodes of typical pulmonary infarction or of thrombophlebitis of the veins of the lower limb were then often seen and helped establish the diagnosis. The clinical picture was not always obscure, inasmuch as there was often a known history of thrombophlebitis and of recurrent pulmonary embolism inadequately controlled by treatment.

Objectively, a right ventricular heave

TABLE 1 **Summary of Clinical Cases**

	Without antecedent heart disease	With arteriosclerotic heart disease	With rheumatic and other forms
No. of cases	11	6	9
Successfully treated	5	6	0
Age at probable onset of embolism	18-88	53-88	36-56
Duration of embolism to time of diagnosis	1 to 10 years	8 weeks to 6 years	2 weeks to 1 year
Venous ligations performed	10 (3 of cava)	5	9 (2 of cava)

and an increased pulmonic second sound seemed significant. Signs of acute pulmonary infarction were sometimes noted.

Outstanding among the laboratory findings were roentgenographic signs of cor pulmonale, as well as changes of old and new pulmonary infarction. These findings have recently been summarized by Fleischner.[6] They include enlargement of the right ventricle, best noted in the lateral film, and an increase in size of the main pulmonary artery and its branches, the latter often forming a plump, tumor-like shadow at the hilum. This is associated with an increased translucency of the affected lobe and an exaggeration in vascular markings in the unaffected lung. The individual emboli in these chronic cases are usually small, and the resultant infarcts are also of no great size. A high diaphragm and blunting of the costophrenic angle by pleural fluid often accompany the acute embolic episode. Old infarcts often leave flat thickenings of interlobar pleura.

The electrocardiogram often showed right ventricular preponderance.

Cardiac catheterization was performed in some cases, particularly to rule out congenital heart disease. A precapillary pulmonary hypertension was the important finding. In several instances, Dr. Eugene Robin and his associates were able to establish the presence of diminished pulmonary artery perfusion.[7,8] Pulmonary function studies by Dr. Roe Wells and his associates were sometimes helpful in ruling out restrictive chest disease as responsible for the cor pulmonale. Surgical exploration to rule out lung tumor or pericarditis has been done occasionally in our hospital, once in this series.

The presenting problem in patients with previously established heart disease was usually the advent of unexplained deterioration, which often took the form of pulmonary edema, sudden arrhythmias, angina, digitalis intoxication, intractable peripheral edema, or fever. These features, singly or in combination, have been emphasized by several authors.[9-14] The onset of symptoms was somewhat harder to date in the rheumatic and miscellaneous patients than in those of the other two groups.

Results of venous ligation. Results of treatment were strikingly different in the 3 groups. Less than half of the purely embolic group, and all of the arteriosclerotic patients, but none of the rheumatic and miscellaneous patients were salvaged. The use of Dicumarol was the only therapy in 1 case of arteriosclerosis, with long-term success. Dicumarol had been used in 3 patients in the group without antecedent heart disease but had failed to prevent further embolism; subsequent ligation did control the disease, however. Ligation of the superficial femoral veins was performed in 2 patients (without success); of the common femoral veins, in 16; and of the inferior vena cava in 5 patients.

Patients successfully treated had no further embolic attacks; their heart failure was resolved, and they resumed their former activities in comfort. Four months after the operation, 1 patient died suddenly from hemorrhage, probably caused by self-administered Dicumarol. The remainder have been followed two to nine years after definitive vein ligation. There was no special feature existing before treatment, except for the 3 major categories, which even in retrospect differentiated the potentially successful candidate from the potential failure.

Patients in the first group labeled as failures died from their heart disease two weeks to nine months after the operation. An additional failure was a man

18 years old at onset of his embolic disease who lived fifteen years after caval ligation but whose heart failure was permanent and progressive.

The patients in the third group all failed to rally after surgery. All but one died within four weeks after operation. The exception lived four years but was hospitalized for progressive heart failure 7 times during that period.

Autopsy was performed in 8 of the failures. In 2 rheumatic patients, embolism was recent and appeared of insignificant degree, but the pulmonary arteriolitis characteristic of mitral disease was present (figure I). These patients are included to emphasize the problem in diagnosis. In 2, there was thrombosis in the right atrium, which was at least a supplementary source of embolism. In all subjects with multiple embolism, there was also the extensive chronic reactive and occlusive disease of the pulmonary arteries and arterioles characteristic of pulmonary hypertension.

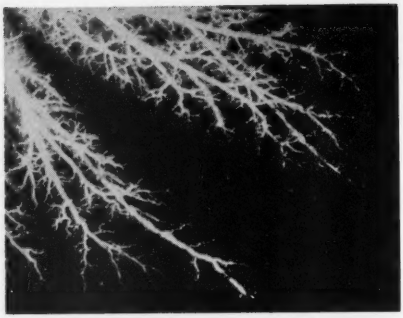

FIG. 1. *Postmortem pulmonary arteriogram in patient with rheumatic mitral disease and no significant embolism. Note extensive partial obstructions of small arteries caused by proliferative arteriolitis. Abrupt loss of fine branching beyond these vessels is also characteristic. (Preparation through courtesy of Dr. George Smith, Pathology Department).*

Pathology

Pulmonary arterial disease. A syndrome of right heart failure due to repeated small emboli was defined by clinicopathologic correlation by Moller in 1923,[11] Belt in 1939,[15] Hampton and Castleman in 1940,[16] White in 1940,[13] and Owen and associates in 1953.[5] Homans,[17] in 1943, recognized and successfully treated several cases by venous ligation. Most of the emboli lodge in the smaller branches of the arterial tree, so that the hypertension is the result of the aggregate of many small occlusions. Pulmonary infarction is minimal. The multiplicity of embolic episodes is attested by the variable age of the emboli found, with organization of varied stages and some fresh emboli.

The evolution of pulmonary embolism into pulmonary arteriosclerosis has been demonstrated by Harrison[18] and confirmed by others.[19, 15] Once the arteriosclerosis develops, the stage is set for a self-perpetuating sclerotic and thrombotic occlusive process, such as exists with arteriosclerosis in other territories. The arteriosclerosis engendered by the emboli leads to pulmonary arterial occlusion, which in turn increases pulmonary hypertension with further arteriosclerosis. Acute pulmonary occlusions, due to thrombosis, will simulate new episodes of embolism.[20]

The cor pulmonale due to pulmonary embolism from leg vein thrombosis is involved in a second vicious circle. Thrombosis of the leg occurs as a complication of the right ventricular failure, giving rise to more pulmonary embolism and further right heart strain.

Pulmonary arteritis, arteriosclerosis, and thrombosis are known to complicate a variety of heart lesions, especially when the disease has led to a low cardiac output. The subject is reviewed by Ball and associates[20] and by Liebow.[19] Mitral valvular disease is particularly

prone to this complication. Factors considered etiologically significant in this connection are a low cardiac output, high pulmonary resistance, and arteritis that is sometimes of the rheumatic variety. It is emphasized that it is often difficult to state whether or not the arterial lesions have been engrafted upon old pulmonary emboli.

Short[21] has demonstrated that pulmonary hypertension from any cause leads to a widespread reactive occlusion of the small pulmonary arteries and arterioles, which in turn enhances the hypertension.

Primary pulmonary hypertension is the name given to a condition in which cor pulmonale is caused by an idiopathic occlusion of moderate-sized and small pulmonary arteries. As silent embolism becomes recognized more frequently, cases belonging in this separate category become ever more rare.[4, 22, 23]

Variable source of the embolus. Most statements on the frequency of various sources of pulmonary embolism are questionable because of the incomplete nature of the usual autopsy. A highly significant report is that of Zeitlhofer and Reiffenstuhl,[24] based on 487 autopsies performed in Vienna on subjects who died of pulmonary embolism. (The patients had been admitted for a variety of medical and surgical problems; the number of cardiac cases was not given.) The authors were satisfied that the source of the embolism was determined in all instances. Their results (table 2) affirm that the veins of the lower extremity or some part of the inferior caval systems was the usual source. The right heart was the source in less than 1 per cent of cases. More recently, Fowler and Bollinger[25] reported from Illinois on a series of 97 cases of pulmonary embolism including 63 cases of heart disease. In this group, the heart was considered the source in 39 per cent (table 2).

All 383 autopsied cases of pulmonary infarcts reported by Franco Browder and associates[26] were of patients with heart disease. They found clots in many places and frequently did not assign a single site as the one responsible for embolization. While the report is deficient in details on the lower extremity veins, it is significant that thrombus was found in the right heart alone in 17.5 per cent and in the right heart plus either the superior or inferior cava in another 2.6 per cent.

It is probable that cardiac patients dying with pulmonary embolism have a chance, probably greater than 20 per cent, of possessing thrombus in the right heart or terminations of both cavae,

TABLE 2 Source of Fatal Pulmonary Emboli

	General autopsy experience		Cardiac patients only
	Zeitlhofer and Reiffenstuhl[24] (per cent)	Fowler and Bollinger[25] (per cent)	Franco Browder[26] et al (per cent)
Lower limbs as source	89.1	20.6	
Pelvic veins or inferior vena cava	10.3	26.6	
Right heart	0.6	39.3	17.5
Right heart plus either cava			2.6
Unknown		13.5	

which may serve as the origin of pulmonary emboli. It is uncertain how many of these thrombi may be terminal—the marantic thrombi of older writers.

Influence of pathology on outcome of treatment. The difference in results in the 3 groups of our patients is due, we believe, to differences in pathology and clinical course before operation. The arteriosclerotic patient is the most favorable, because the basic disease does not involve the pulmonary arteries and the heart is not seriously impaired during the resting state except for the isolated acute episodes of coronary occlusion. The relatively good health between such attacks allows a sharp delineation of the symptoms of pulmonary embolism. Finally, there is little likelihood that the thrombus responsible for the embolism is located in the right heart rather than in the peripheral veins.

By contrast, the patient with rheumatic or congenital heart disease is chronically ill as regards the heart, as well as the pulmonary arteries and arterioles. It is more difficult to separate symptoms due to this chronic illness from those due to pulmonary embolism; there is considerable chance for thrombus to exist in the right heart with or without peripheral venous thrombosis; finally, even when a ligature is placed proximal to the offending thrombus, the patient is left with his basic progressive heart and pulmonary arterial disease.

In the patients with cor pulmonale due to embolism alone, sufficient progressive disease has been set up in the pulmonary arteries to explain the position of this group's being, with respect to results of treatment, halfway between the other two.

Anatomic and technical considerations

Femoral vein. The pattern of the femoral venous system was reported in some detail by Edwards and Robuck[27] (figure II). It was found that, in 10 per cent of subjects, the deep femoral vein commenced by a large connection with the superficial femoral in the lower adductor canal. This communication is the basis for the anomaly seen in figure IID, a condition which if not present before operation is probably approximated, in most instances, some months after a ligation of the superficial femoral vein. We have had occasion to ligate the common femoral veins in 8 patients in whom previous superficial femoral vein ligation had only temporarily interrupted recurrent pulmonary embolism. In all instances, the second procedure at the common femoral level appeared to control the situation permanently. One of these patients is included in the category of embolism with arteriosclerotic heart disease in this report. She lived free of embolism for nine years after the common femoral ligation, dying from an acute coronary thrombosis.

The presence of an existing or potential gross bypass of a ligation of the superficial femoral vein has led us routinely to ligate the common rather than the superficial femoral in instances of pulmonary embolism. The swelling of the limb which has been feared after common femoral ligation has been largely obviated through the placing of the ligature just proximal to the confluence of the superficial and deep femoral veins (lig., figure IIA). The ligature is thus distal to the circumflex veins and impedes less blood than if it were proximal to them. This diminishes early postoperative pooling of blood and lessens later swelling. The circumflex vessels have a course that is mainly transverse and do not constitute a route for the passage of emboli from the calf. Placing the ligature close to the distal limit of the lateral circumflex presents the formation

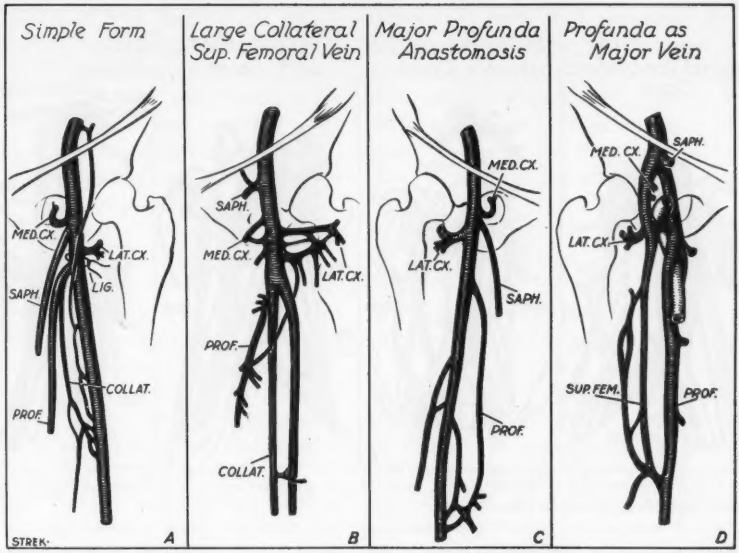

FIG. 11. *Variations in femoral venous pattern (after Edwards and Robuck*[27]*).*

of a distal cul-de-sac of femoral vein and mitigates against the formation of a clot proximal to the ligature. In this respect, it is also important not to manipulate the vein proximal to the ligature site.

The saphenous vein, if grossly varicosed or thrombosed, should be divided concomitantly with the femoral vein. In spite of the warnings against such a procedure voiced in older textbooks, no special difficulty from the simultaneous division of the two veins can be detected. Finally, in patients with heart failure, heparin therapy is begun on the operating table at the moment of ligature to reduce the chance of proximal thrombosis. In all instances, unless a special contraindication exists, heparin is given postoperatively to diminish distal thrombosis, thus minimizing postphlebitic and postligation sequelae in the limb.

Inferior vena cava. Recurrence of embolism after caval ligation is often suspected. Possibilities include transport via a left cava or caval rudiments or by collaterals of the cava and embolism from thrombosis in tributaries terminating proximal to the ligature. We are aware of proved recurrence based only upon thrombosis of one tributary, the ovarian vein. Nevertheless, mention should be made of the other possibilities.

Major variations of the inferior vena cava pertinent to the present thesis are those existing in its infrarenal segment[28] (figure III). In instances of sinistrality of the cava, the surgeon will fail to find the vessel on the right side and must then explore the left. Duplication of the cava may be difficult to detect, since it is only by deciding that the right cava appears inadequate in size that the surgeon will be led to assume that an additional left-sided vessel exists. Because there are numerous instances of lesser degrees of bilaterality (figure IV), the existence of this pattern constitutes a possible defect in the control of em-

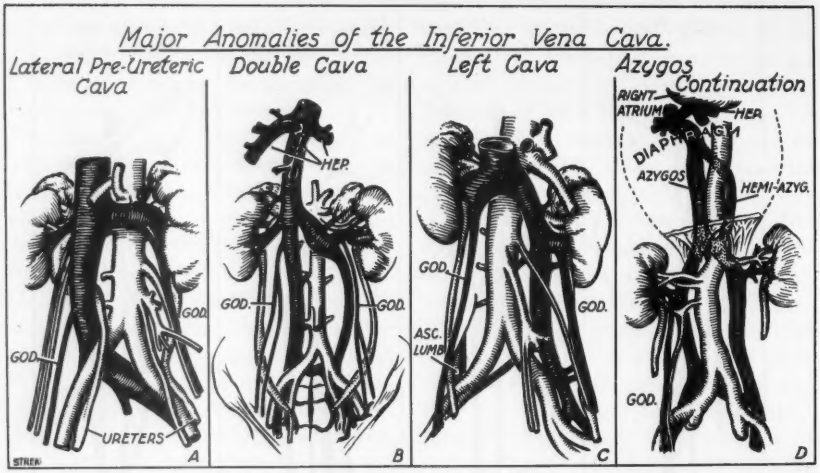

FIG. III. *Major anomalies of inferior vena cava.* God.= *gonadal vein (A, C, after Gladstone; B, after McClure and Huntington, in Edwards[28]).*

bolism by ligation. A final problem is that of the pelvic kidney (figure IV), since ligation of the cava above this viscus would appear to carry a substantial hazard of kidney failure or of the development of nephrosis.

Collaterals of the cava, as revealed in a study being currently pursued,[29] may be of a size adequate to transport large emboli. For the most part, however, these collaterals either begin or end by a reticulate anastomosis, which would prevent embolic transport. The ascending lumbar vein is an exception, since it may be a wide vessel from origin to termination.

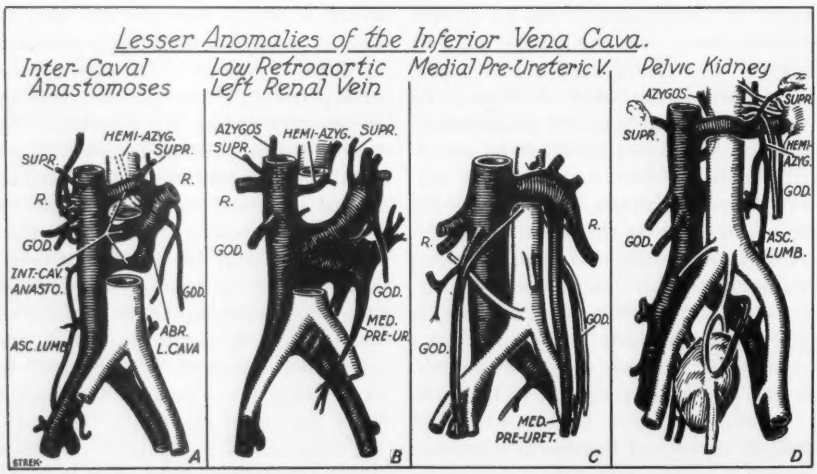

FIG. IV. *Lesser anomalies of inferior vena cava (after Edwards[28]).*

We know of one instance in which the ovarian vein was responsible for death from embolism after caval ligation. In one of our own cases, signs of pulmonary infarction recurred after caval ligation done elsewhere, and surgical exploration disclosed widened and thrombosed ovarian veins. Recovery followed their division. It would thus appear desirable to ligate the ovarian veins concomitantly with the cava in multiparous women. The right ovarian vein is available in the usual retroperitoneal approach to the cava. Simultaneous ligation of the cava and both ovarian veins requires a transperitoneal approach, which carries a somewhat higher morbidity than the retroperitoneal.

As with femoral vein ligation, heparin given postoperatively will diminish the extent of thrombosis distal to the ligature.

Proposed plan of treatment of postembolic cor pulmonale

The treatment of the acute episode of infarction, and of the failure, is essentially the same as for these disorders in any setting. A major aim of treatment is the prevention of further emboli. As mentioned earlier, a major portion of the pulmonary arterial tree is already obstructed by the time the diagnosis is made, leaving little margin for error. For this reason, we feel that anticoagulant administration is a poor choice of therapy and that venous ligation should be done as soon as the diagnosis is reasonably certain.

When a diagnosis of thrombophlebitis can be made on the basis of local physical signs, in all 3 categories of patients, ligation of the common femoral veins is usually adequate if no thrombus is present at the site of ligation.

A decision should be reached before operation whether to perform a caval ligation at once if a thrombus is unexpectedly found in the femoral vein and cannot be easily extracted or if there is a strong suspicion of pelvic vein thrombosis. Caval ligation is a more major undertaking than femoral ligation. It requires general anesthesia and is often more than a sick cardiac patient can withstand. A day or two spent in improving the cardiac status, utilizing the good, if imperfect, protection of heparin, will often bring the patient to the operating table in better condition.

In patients without positive evidence of the source of embolism, our present practice varies according to the category of disease. In patients without antecedent heart disease, with established arteriosclerotic heart disease, or with a diagnosis of primary pulmonary hypertension, we are inclined, at present, to ligate the inferior vena cava. In patients with rheumatic heart disease, anticoagulant treatment is undertaken, unless the pulmonary signs of infarction are unmistakable or if local signs of venous thrombosis become evident on further observation.

Summary

Twenty-six cases of pulmonary embolism recurring for at least six weeks before the institution of definitive treatment and followed for at least two years are described. There were 11 cases without underlying heart disease, 6 with arteriosclerotic heart disease, and 9 with rheumatic and miscellaneous types of heart disease.

The difficulty of recognition of pulmonary embolism is emphasized, especially in patients with heart disease whose symptoms mask embolic episodes.

The site of origin of thrombi is discussed, and 2 vicious circles are described in which (1) embolism produces pulmonary hypertension, followed by pulmo-

nary arteriosclerosis, thrombosis, and more pulmonary hypertension and (2) embolism produces right ventricular failure, thrombosis of the leg veins, and more embolism.

Definitive treatment to prevent further embolism was shown to be relatively effective in patients without antecedent underlying heart disease and in those with arteriosclerotic heart disease but relatively ineffective in those with rheumatic or miscellaneous heart disease in whom chronic intractable congestive heart failure was present.

Variations of venous anatomy as applied to surgical therapy are described, and a plan of management of this problem is discussed in detail.

Presented at the annual meeting of the American Heart Association, St. Louis, October 22, 1960. This work was supported by a grant from the Milton Fund, Harvard University.

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editorial

When grief strikes at the aged

■ It is hard enough for a young man or woman to rise up after having been struck down by great grief. Often it is almost impossible for the person to recover when the blow comes in the later years, for then there may be no hope for future improvement. One of the best discussions of this subject that we have seen is in chapter 12 of Professor Granger Westberg's new book on "Minister and Doctor Meet." Granger Westberg is associate professor of religion and health at the University of Chicago. He is a devoted and able minister who for several years has been teaching hospital chaplains what they can do to help doctors. Naturally, when Westberg started his work some doctor did not want a nonmedical man talking to their patients about more or less medical problems, but eventually most of the doctors were won over; they found that Westberg and his group could help them and soon they were asking him to see troubled and grieving patients.

As Professor Westberg says, the way in which a person grieves over the loss of something important in his life can have a remarkable effect upon his health. This fact should more often be brought home to physicians. They may not know what grief is doing to a woman who has lost her uterus, or a breast, or an only child, because they haven't talked to her. In some cases, a great grief becomes pathologic. I remember a beautiful woman of 50 who went all to pieces nervously and physically when her aged mother died. The daughter had been so devoted to her mother that she had never bothered to go out with men and had never married. Naturally, when the mother passed away the poor woman felt that life for her had ended, and she felt that the sooner she died the better.

Professor Westberg says that ministers see cases in which much harm comes to people who have been overwhelmed with grief. According to him the typical stages of grief are: (1) shock, (2) emotional release, (3) inability to concentrate on anything but the lost object, (4) symptoms of physical distress, (5) feelings of depression and gloom, (6) a sense of guilt, (7) a sense of hostility, perhaps to the doctor who was taking care of the patient when he died, (8) unwillingness to go back into a normal life, (9) gradual realization that withdrawal from life is unrealistic, and (10) readjustment to reality.

The old person overwhelmed with great grief may stop sleeping and may not eat properly. The result will be a loss of weight and often a functional illness of some type. Many of these people feel that there is no further reason for continuing to live, and hence they become decidedly depressed. Some think of suicide. Many don't want to be cheered up. Many feel guilty when they think of the times when they were unkind to the person who is gone. When the person feels guilt in the religious field, his minister may be the man most likely to help him. The minister must try to impress him with the fact that God forgives.

Often the chaplain can help by trying to convince the grieving person that the doctor could not possibly have saved the

one who died, no matter what he might have done. The minister can help much also by encouraging the person to go back into his usual activities. Nothing helps so much as work, which can keep the old person from withdrawing from life. He must readjust to reality. He must start going out again, to visit with old friends. Perhaps he must learn to pray again. Often it is very difficult for a chaplain or a physician or even a psychiatrist to know how to talk to one of these persons. Certainly no one should ever get to arguing acrimoniously with these people or scolding them.

Everyone—doctor, minister, nurse, or relative—who comes in contact with the sick could be greatly helped by reading this remarkable book which is so full of wisdom.

WALTER C. ALVAREZ, M.D.

CURRENT COMMENT

Age and the ring

■ Any old-timer watching the recent Archie Moore–Rinaldi prize fight must have had mixed emotions. Here was Moore, 47 years old according to his mother, against Rinaldi, who was 26 and young enough to be Moore's son. Every old-timer would naturally hope that Moore would stand up creditably against his younger opponent, but at the same time, every old-timer must have felt that the odds certainly were against him. Actually, the vigorous fight went on for 15 grueling three-minute rounds, and Moore won easily by unanimous decision of the judges.

Rinaldi, a husky and alert young Italian, fought hard and well. Moore, however, had clearly the greater experience and the greater wisdom from that experience. Moore did not waste motion. He conserved his strength by relaxing fully when his great arm and shoulder muscles were not actually in action. Furthermore, he was as skillful in dodging and ducking the swings of his opponent as he was in putting his lightning-fast punches into the places that hurt. Even more impressive was Moore's good will at the end of the contest. Actually, he and Rinaldi almost embraced. Then Moore stated what he hoped to do with some of the money that he had won. Part of it would go to help blind and deaf children. Some would go to aid the Freedom Riders. And some would go to B'nai B'rith. Moore is clearly a Negro with well-balanced mental and physical health.

The stiff competition of American athletics usually means that a player is out of the game sometime during his 30s. Boxing is the roughest and most demanding of all games. Yet the Moore-Rinaldi fight demonstrated clearly that a man well in his 40s, who has maintained good mental and physical health, can hold his own successfully against a younger and much more vigorous person. Perhaps the slow accumulation of experience and wisdom with aging does help. The fighting rounds of life go on day after day, and usually one's fighting opponents get younger, tougher, and more alert. Maybe Archie Moore has something that might help us all as we fight along. This seems chiefly to be that ancient ideal of a sound and healthy mind in a sound and healthy body. This combination is worth every effort in striving to maintain all during one's life.

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*Bickerman, H. A., et al.: Physiologic and steroid therapy in respiratory disease, Scientific Exhibit, A. M. A. Convention, Atlantic City, N. J., June 8-12, 1959.

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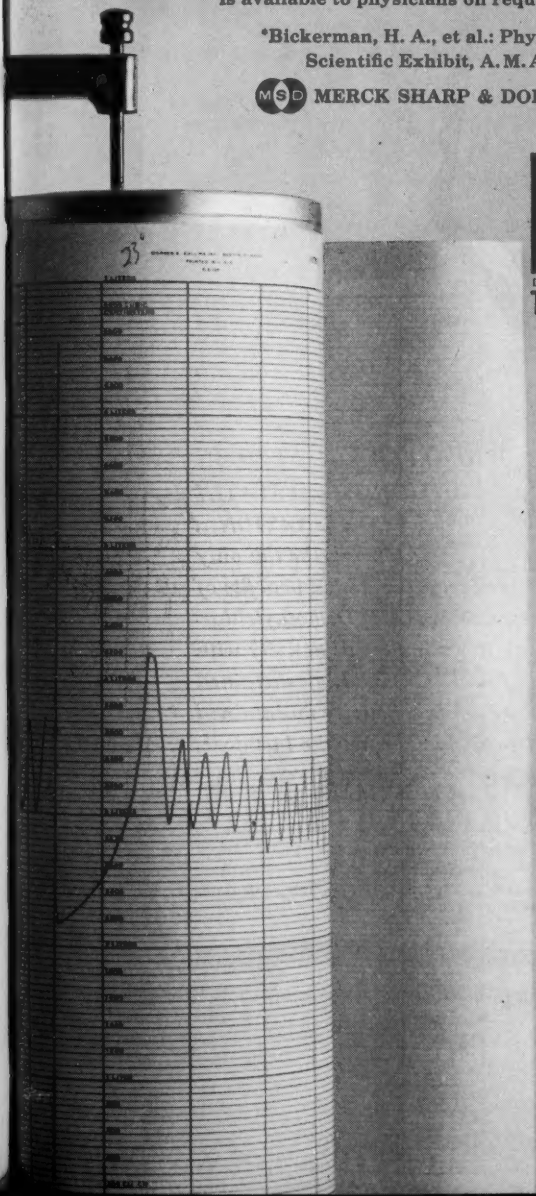

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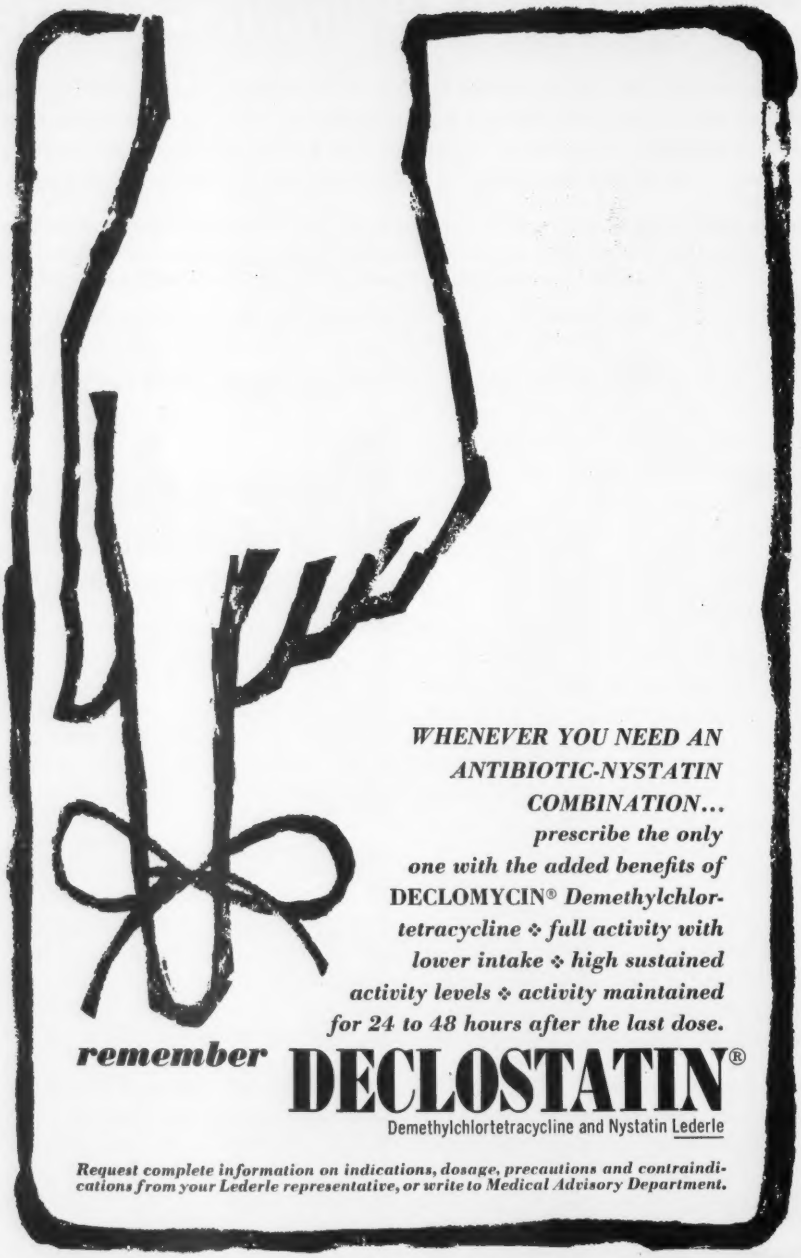
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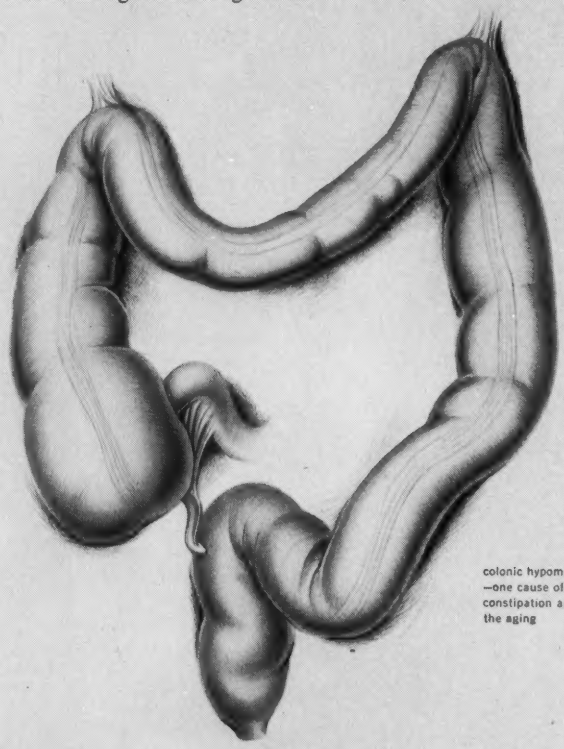

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ORIGINAL RESEARCH SERVING THE PHYSICIAN

SANDOZ

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activities and announcements

Future Meetings

The eleventh International Conference of Social Work will be August 19 through 25, 1962, in Rio de Janeiro, Brazil. Several meetings will be devoted to the comparison of practice in geriatrics and gerontology.

The Canadian Association of Physical Medicine and Rehabilitation will hold its ninth annual meeting August 24 to 26 at the Bessborough Hotel, Saskatoon, Saskatchewan. Details may be obtained from the Association office, 6265 Hudson Road, Montreal 26, Quebec.

The International Association of Gerontology European Research Committee for Clinical Medicine meeting at The Hague, The Netherlands, September 12 to 16 will feature discussions of "Age and Mental Abnormality," "Age and Cancer," "Age Disturbances of Haematopoiesis," and "Problems of Old Age."

The National Rehabilitation Association annual conference will be October 2 to 4 at the Whitcomb Hotel, San Francisco.

The American Psychiatric Association Mental Hospital Institutes will be held October 16 through 19 at the Hotel Sheraton-Fontenelle, Omaha.

The American Public Health Association annual meeting in conjunction with those of about 60 related organizations will be at Cobo Hall, Detroit, November 13 through 17. Medical care for the aged, community health, prevention of disease, and environmental health will be discussed.

The National Society for Crippled Children and Adults will hold its annual convention November 17 through 21 at the Denver-Hilton Hotel, Denver. Conclusions from a two-year study by representatives of 50 national organizations on the elimination of architectural barriers to cripples using public and private buildings will be reported. A leg-ankle brace developed at the Biomechanics Laboratory of the University of California Medical Center, San Francisco, will be demonstrated.

The American Public Welfare Association National Biennial Round Table Conference is scheduled for November 29 to December 2 in Chicago. Topics will include gerontology and geriatrics.

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WGS Officers

Dr. Margaret Gordon, acting director of the Institute of Industrial Relations of the University of California at Berkeley, is the new president of the Western Gerontological Society. Other officers are Dr. Harry Sobel, director of Research on the Biochemistry of Aging at St. Joseph's Hospital, Burbank, California, president-elect, and Mrs. Mercia Kahn, district manager of the Social Security Administration, San Francisco, secretary-treasurer.

(Continued on page 64A)

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activities (Continued from page 62A)

Institute on Housing

The Institute on Producing Housing for Older People, sponsored by the National Council on the Aging and the Institute of Physical Medicine and Rehabilitation (IPMR) of the New York University Medical Center, in cooperation with the National Housing Center, was held March 26 through 28 at the IPMR in New York City. A group of builders and developers who produce sales housing for older persons attended lectures and meetings on opportunities for the building industry in housing older persons; the economic, social, and physical requirements of older people in housing and living arrangements; site selection and development; architectural planning; community facilities and services; financing housing for older persons; and constructing and equipping housing appropriate to the needs of the elderly. A special feature was three concurrent clinics on environmental planning, designed to help builders solve the practical problems involved in producing housing for older persons.

•

Society for Gerontologic Psychiatry

The Boston Society for Gerontologic Psychiatry, Inc., was incorporated in July 1960 to provide a source of consultation, research, and teaching based on psychoanalytic principles. Charter members of the organization are Dr. Martin Berezin, president; Dr. Edmund C. Payne, Jr., vice-president; Dr. Stanley H. Cath, secretary; and Dr. Eliot Landsman, treasurer. A symposium, The Normal Psychology of the Aging Process, was held by the society in January 1961.

•

Nursing Home Design

The modern concept of the nursing home is changing, according to speakers at a meeting of the New York Chapter of the American Institute of Architects held on April 6. Miss Ollie Randall, vice-president of the Na-

(Continued on page 68A)

Diagnosis: Varicosity

Partial or full treatment: Freeman Full-fashioned elastic stockings

Thromboembolic disease of the legs that requires extra control is effectively treated with Freeman's reinforced Astarte stockings. Modified control for less severe cases is assured with Freeman's sheer stockings. Uniform pressure from top to toe. Hand finished self-edge knitted open toe prevents uncomfortable binding—increases comfort of patients. Also full-foot styles with Helenca stretch toe.

Adequate support and uniform compression are provided only by natural rubber Full-Fashioned stockings.

Full-thigh, half-thigh, knee and garter hose lengths.

Prescribe Freeman with Confidence.

Freeman MANUFACTURING COMPANY, DEPT. 558, STURGIS, MICHIGAN

This arthritic patient felt much better on Dianabol®

Mrs. K. S., 73, complained of severe pain in lower back. Diagnosis: osteoarthritis and osteoporosis. Steroids and analgesics gave only moderate relief. Gradual weight loss continued. Dianabol, 10 mg./day, started. "Within a week symptomatic improvement had begun." Patient gained strength, agility, and sense of well-being. Photograph used with patient's permission.

Please turn page

Why arthritic patients feel much better on Dianabol

1. In arthritis, Dianabol improves general physical condition

Arthritis, like other chronic illnesses, plunges the body into a catabolic state. Protein stores are depleted; appetite wanes; weight drops; strength and vigor decline. By aiding the deposition, synthesis and utilization of protein, and by conserving calcium, Dianabol promotes lean weight gain, increases strength and vitality, and strengthens bone structure in patients with a wide range of chronic diseases. Recent studies show that adjunctive use of Dianabol may be particularly valuable in patients with arthritis to improve over-all clinical status. Kuzell and Naugler,[1] for example, report that arthritic patients on Dianabol "generally have experienced an increase in appetite, weight, strength and endurance." Kuzell and Naugler note further: "Unlike some other testosterone derivatives, the use of this compound [Dianabol] is not followed by virilizing phenomena. Fluid retention has been no problem."

2. In arthritis, Dianabol helps restore a sense of well-being

Plagued by pain and reduced mobility, arthritics often lose hope and become depressed. The marked improvement in general health usually associated with therapy with Dianabol may have a favorable effect in these patients, as it has in so many chronically ill individuals. As physical status improves, hope is revived and a sense of well-being restored. Commenting on the use of Dianabol in a group of debilitated, cachectic patients, Gingrich[2] states: "The majority of patients experienced increase in appetite and a feeling of well-being."

3. In arthritis, Dianabol augments the beneficial effects of salicylates, corticosteroids, etc.

Several investigators[1,3,4] have observed improved therapeutic response after the addition of Dianabol to antiarthritis regimens. Kuzell and Naugler[1] state: "In generalized osteoarthritis, symptoms have been less bothersome, and in ankylosing spondylitis gain in weight and strength has followed the use of Dianabol." Clark,[3] reporting on 12 hospitalized patients with rheumatoid arthritis being given moderate to large doses of corticosteroids with evidence of steroid intoxication, noted that the addition of Dianabol promptly decreased joint symptoms but increased steroid intoxication. However, with Dianabol it was possible to reduce corticosteroid dosage considerably, while maintaining and even furthering clinical improvement. In 15 ambulatory patients on small maintenance doses of corticosteroids, the addition of Dianabol resulted in further clinical improvement which was continued even when corticosteroid dosage was reduced in some cases.[3,4]

4. In arthritis, Dianabol counteracts the catabolic effects of corticosteroids

Prolonged use of corticosteroids may result in excessive breakdown of protein in all tissues, including bone,[5] as well as undue phosphorus and calcium loss.[6] If protein destruction is allowed to go unchecked, it may lead to osteoporosis—a condition that has occurred with increasing frequency in patients receiving corticosteroids for extended periods.[7]

Tillis[5] asserts that it is "imperative" to restore the protein bone matrix in such patients

through the use of an anabolic agent. He studied the specific anabolic benefits of Dianabol in 50 patients with osteoporosis (34 postmenopausal and 16 corticosteroid-induced), most of whom also had rheumatoid arthritis. Dianabol relieved bone pain, increased strength and vigor, and induced a sense of well-being in 41 (82 per cent) of these patients. Edema, observed in 8 patients, was cleared in 4 by reduction of dosage; the remaining 4 responded promptly to hydrochlorothiazide. Gastric distress was noted in 2 patients, slight hoarseness in 1 woman, and facial acne in 1 woman. Other investigators[8,9] have shown that addition of Dianabol to the regimens of patients receiving corticosteroids improved nitrogen and potassium metabolism and reduced phosphorus and calcium losses. Reporting on 10 patients taking corticosteroids, most of whom had corticosteroid-induced osteoporosis and/or myopathy, Abbott[9] states: "In the patients who showed a markedly negative nitrogen balance the administration of 10 mg. of Dianabol per day greatly reduced the protein deficit. In others who were eating well and taking smaller amounts of corticosteroids a positive nitrogen balance resulted which increased with Dianabol." Abbott notes that creatinuria, which occurred on corticosteroids alone, was increased by Dianabol, as it is by methyltestosterone and the newer oral methyl- or ethyl-testosterone derivatives. However, he observes that the "significance of this creatinuria is not known and no ill effects have been ascribed to this change." While the finding of elevated serum aldolase levels raised the theoretical possibility of potentially deleterious effects, Vignos *et al*[8] and Abbott[9] noted no androgenic or myopathic effects and no liver disorders in patients who took Dianabol and corticosteroids for up to 8 months. Kuzell and Naugler[1] state it is their impression that Dianabol has checked weight loss following prolonged administration of triamcinolone in patients with rheumatoid arthritis. They add that, with Dianabol, protein patterns have migrated toward normal profiles, purpura consequent to corticosteroid administration has been lessened, and the erythrocyte sedimentation rate has been diminished.

REFERENCES: 1. Kuzell, W. C., and Naugler, W. E.: Paper presented at the Annual Meeting of the American Rheumatism Association, Hollywood-By-The-Sea, Florida, June 9-11, 1960. 2. Gingrich, G. W.: Clinical report to CIBA. 3. Clark, G. M.: Paper presented at the Seventh Interim Session of the American Rheumatism Association, Dallas, Texas, Dec. 10, 1960. 4. Clark, G. M., Kaplan, S., Goobar, J., and Mills, D.: Arthritis and Rheumatism *4*:106 (Feb.) 1961. 5. Tillis, H. H.: Clin. Med. *8*:274 (Feb.) 1961. 6. Lockie, L. M.: J.A.M.A. *170*:1063 (June 27) 1959. 7. Boland, E. W.: J.A.M.A. *150*:1281 (Nov. 29) 1952. 8. Vignos, P. J., Jr., Abbott, W. E., Post, R. S., and Levy, S.: J. Lab. & Clin. Med. *56*:954 (Dec.) 1960. 9. Abbott, W. E.: Research report to CIBA. 10. Misurale, F.: Minerva med. *51*:996 (March 21) 1960.

advantages of Dianabol over other anabolic agents as an adjunct in the treatment of arthritis

▪ *Dianabol has an exceptionally favorable anabolic/androgenic ratio.* The anabolic effects of Dianabol occur at dosages which generally preclude androgenic side reactions. In this respect, Dianabol has proved superior to 12 other anabolic compounds.[10] Laboratory evidence also indicates that Dianabol has no estrogenic, progestational, or corticoid-like activity which might be clinically detrimental.

▪ *Dianabol is economical.* Low in cost, Dianabol is especially suitable for arthritic patients who usually require long-term therapy.

▪ *Dianabol is effective orally.* Because it is an oral preparation, Dianabol spares patients the inconvenience and discomfort of parenteral drugs.

Dianabol®

low-cost, oral anabolic agent

an important new ally in the treatment of arthritis

Other indications for Dianabol:

- Underweight, debility and weakness
- General physical weakness and cachexia due to chronic diseases
- Retarded convalescence from illness, surgery, fractures, wounds, and burns

For complete information about Dianabol (including dosage, cautions, and side effects), see 1961 Physicians' Desk Reference or write CIBA, Summit, N. J.

SUPPLIED: *Tablets,* 5 mg. (pink, scored); bottles of 100.

DIANABOL® (methandrostenolone CIBA)

CIBA
SUMMIT, NEW JERSEY

2/2964MB

 (Continued from page 64A)

tional Council on the Aging, said architects must educate their clients to incorporate advances in architectural design which help the aged to live longer and happier lives. The nursing home should be designed as a place to live as well as a treatment center, providing privacy and allowing patients to move about freely.

•

Dental Society Survey

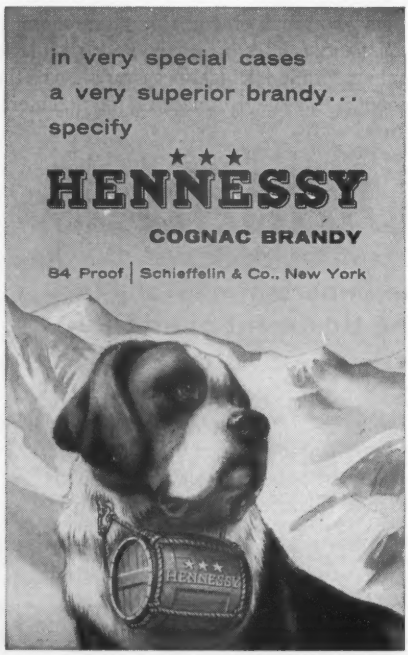
Among the activities of state dental societies to determine and meet dental needs of the aged and chronically ill, according to a recent survey conducted by the Council on Dental Health of the American Dental Association, are (1) participation in state joint councils to improve health care of the aged; (2) specific allocation of responsibility for programs in the field of aging to a particular group within the society; (3) participation in pre-White House Conferences; (4) surveys of hospitals, nursing homes, and component societies in regard to dental care needs of the aged; and (5) special activities for members, such as programs at state meetings and conferences, workshops, and articles in state dental journals and other publications. In general, comments and reports by 48 of the 54 surveyed societies reinforced the position of the A.D.A. Council on Dental Health that "the most realistic approach to solving problems in dental care of the aging is through preventive dentistry with a life-long program of dental care."

•

Retirement Community in Arizona

Wickenburg, a town of about 3,500 in north central Arizona, is the location of this state's newest retirement community. Planned and constructed by a Phoenix contracting and development firm, the single-family homes will range in price from $9,000 to $11,500, with 90 per cent conventional twenty-five-year mortgages available to persons of any age.

(Continued on page 70A)



AT ANY AGE
A
SAFE
APPROACH
IN THE TREATMENT OF PSORIASIS

RIASOL

Clinically tested, safe and effective RIASOL offers maximum assurance against recurrence and adverse reactions.
RIASOL contains 0.45% Mercury chemically combined with soaps, 0.5% Phenol, and 0.75% Cresol. Available at pharmacies or direct in 4 and 8 fluid ounces. *Write for professional sample and literature.*

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For the irritable G.I. tract

Milpath acts quickly to suppress hypermotility, hypersecretion, pain and spasm, and to allay anxiety and tension with minimal side effects.

AVAILABLE IN TWO POTENCIES

MILPATH-400—Yellow, scored tablets of 400 mg. Miltown (meprobamate) and 25 mg. tridihexethyl chloride.
Bottle of 50.

Dosage: 1 tablet t.i.d. at mealtime and 2 at bedtime.

MILPATH-200—Yellow, coated tablets of 200 mg. Miltown (meprobamate) and 25 mg. tridihexethyl chloride.
Bottle of 50.

Dosage: 1 or 2 tablets t.i.d. at mealtime and 2 at bedtime.

Milpath®

®Miltown + *anticholinergic*

WALLACE LABORATORIES *Cranbury, N. J.*

activities (Continued from page 68A)

Gerontology Courses

The Committee on Human Development at the University of Chicago offered four courses in gerontology during the spring quarter, March 27 to June 9: Human Development in Adulthood and Old Age (Dr. Bernice Neugarten); The Aged in American Society (Dr. Ethel Shanas); Adult Roles in Non-Western Family Systems (Robert A. LeVine); and Seminar: Research in Middle Age and Aging (Dr. Bernice Neugarten).

•

Senior Citizens Job Placement Bureau

The Senior Citizens Placement Bureau in Montclair, New Jersey, has been set up to provide free employment services for people over 60 in part-time and occasional jobs. Sponsored by the Junior League and the Community Welfare Council, the Bureau has received a favorable response and a number of placements have already been made.

Brown University Project

Brown University, Providence, Rhode Island, is planning a university-wide center to study the socioeconomic factors associated with aging and the relationship between these factors and the medical and biologic aspects of aging and old age. The project will be supported by a grant from the Division of General Medical Sciences, National Institutes of Health.

•

Stroke Rehabilitation

Lane County, Oregon, has started a 3-step stroke rehabilitation project on a $10,000-a-year budget. Sponsored by the county medical society and financed with federal grants through state and county health departments, the project aims at getting stroke victims back on their feet—at least enough to meet such daily needs as feeding and dressing themselves.

Under the plan, private doctors refer recent stroke patients to Sacred Heart Hos-

(Continued on page 72A)

PROSTALL®

REDUCES PROSTATIC HYPERTROPHY

PROSTALL shrinks the enlarged prostate, without surgery, by local decongestion and de-edematization.

Each capsule contains 6 gr. of a biochemical combination of glycine (aminoacetic acid), alanine and glutamic acid.

ABSOLUTELY SAFE

No toxicity, no side-effects, no contraindications ever reported after use in thousands of cases.

RELIEVES PROSTATIC SYMPTONS

PROSTALL relieved nocturia in 95% of cases, urgency in 81%, frequency in 73%, discomfort in 71%, and delayed micturition in 70%. Benefits improved by continued use.

CONTROLS PROSTATIC HYPERTROPHY

PROSTALL reduced the enlarged prostate in 92% of cases, to normal size in 33%, as determined by rectal palpation.

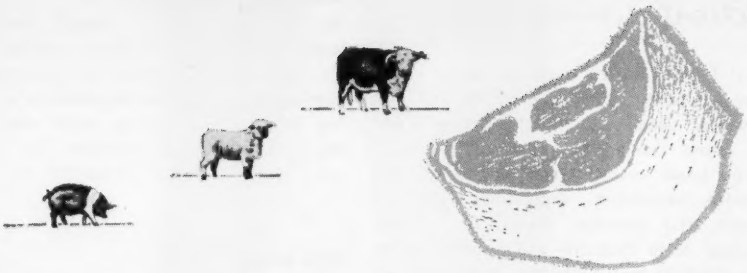
CONTROLLED CLINICAL INVESTIGATION

As reported in the March 1958 issue of The Journal of The Maine Medical Association and in the February 1959 issue of Southwestern Medicine, a controlled clinical investigation of PROSTALL Capsules showed effective results as indicated. Reprints on request.

DOSAGE: 2 capsules t.i.d. after meals for 2 weeks, then 1 capsule t.i.d. for 2 months or longer.

AVAILABILITY: In bottles of 100 and 250 capsules. At all druggists. If your druggist is out of stock, he can order Prostall from his wholesaler.

METABOLIC PRODUCTS CORP. • 37 HURLEY STREET, CAMBRIDGE, MASS.



Why meat animals are modernized

New concepts in human nutrition must be met, whatever they are!

A few years ago everyone seemed to prefer fat type, well marbled meat. Today, the demand is for less fat, more lean meat.

To change animals is not easy.. and it has required years of scientific development. Through careful breeding, specialized feeding and continuing research, livestock men now are raising more and more lean-meat animals...modern animals!

"Just what the doctor ordered."

Through further research and modernized methods, such as tenderizing and closer trim, processors cooperate to bring to retail stores the flavorful, appetizing meat on display everywhere...so attractive to all.

MEAT—*a universally preferred source of*
HIGH QUALITY PROTEIN

AMERICAN MEAT INSTITUTE

MAIN OFFICE, CHICAGO • MEMBERS THROUGHOUT THE NATION

pital for about two weeks of initial group therapy, after which the patient receives advanced therapy at Sunset Nursing Home for about two weeks and then either returns home or is transferred to another nursing institution, depending upon his health and personal situation. A 3-man medical team evaluates the patient's progress. Patients financially able pay their own way.

•

Cancer Center

Both laboratory and clinical research programs involving all phases of the study of cancer will be included in the new Fox Chase Center for Cancer and Medical Sciences, now in the planning stages in Philadelphia. The facilities and personnel of The Institute for Cancer Research and Jeanes Hospital will be pooled as a nucleus for the new center. The 3-phase building program involves expansion of the institute's present laboratories; construction of a 50-bed clinical unit for the study and treatment of cancer patients, which will connect the institute and the hospital; and construction of a conference and seminar building with dining facilities. The National Institutes of Health is providing $750,000, to be matched dollar for dollar, for construction of the additional laboratories and a new animal colony building.

•

Coordination of Studies

During the White House Conference on Aging, representatives from Iowa, Kansas, Minnesota, Missouri, Nebraska, and North and South Dakota agreed on a plan to coordinate analyses of surveys and research reports on aging done in that region. Dr. Arnold Rose, University of Minnesota sociologist, acted as temporary chairman and Dr. Marvin Taves, University of Minnesota sociologist, was elected president. Further discussion on the project is planned during the spring meeting of the Midwestern Sociological Society in Omaha.

Gerontology Curriculum

Mt. Angel College, Mt. Angel, Oregon, a small religious school with a nursing home on the campus, is setting up a gerontology curriculum to train undergraduates in nursing home administration, social work with the aged, and similar activities. The college has a $144,675 federal grant for the work.

•

NIH Grants

Award of 64 grants totaling $1,427,883 to private institutions for research in various aspects of aging has been announced by the National Institutes of Health. Grants were made to investigators in 25 states, the District of Columbia, and the University of Cape Town, South Africa. Of the total, 23 grants are continuations of previous projects, while 41 are new.

•

Elimination of Age Barriers

Pennsylvania's Governor David L. Lawrence has urged state employers to help eliminate age barriers to employment. A letter and brochure, "Good Employing Practices," giving reasons why employers should disregard age when hiring were mailed to about 60,000 individuals, each employing at least eight persons.

The first return replies and comments have been running about 10 to 1 in favor of older workers because they have "favorable experience," are "more reliable and sensitive," and "more dependable, energetic, and willing."

•

New Tax Form for the Aged

Tax form 2948, which allows more liberal deductions for medical expenses for persons 65 and over in reporting 1961 federal income taxes, has been issued by the U. S. Internal Revenue Service. In clarifying instructions for Forms 1040 and 1040W, the new form permits the medical expenses of a dependent parent 65 or over to be deducted without being reduced by 3 per cent of adjusted gross income. As in the past, if

(Continued on page 76A)

Metamine®
(trolnitrate phosphate, Leeming, 10 mg.)
Sustained

In coronary insufficiency

helps you dilate the coronaries

In pharmacologic studies at Pasteur Institute and McGill University, the vasodilator activity of trolnitrate phosphate (METAMINE) was found to be equal or superior to that of nitroglycerin, and of much longer duration.[1-2]

In coronary insufficiency, one METAMINE SUSTAINED tablet q. 12 h. markedly reduces the number and severity of anginal attacks and increases exercise tolerance, with virtual freedom from nitrate side effects and less danger of a forgotten dose.[3-4] Bottles of 50 and 500 tablets.

Thos. Leeming & Co. Inc.

New York 17, N. Y.

1. Bovet, D., and Nitti-Bovet, F.: Arch. Internat. de pharmacodyn. et therap. 83:367, 1946. 2. Melville, K.I., and Lu, F.C.: Canad. M.A.J. 65:11, 1951. 3. Fuller, H.L. and Kassel, L.E.: Antibiotic Med. & Clin. Therapy 3:322, 1956. 4. Eisfelder, H.W. et al.: J. Am. Geriatrics Soc. 8:62, 1960.

1 tablet all day

1 tablet all night

Peri-Colace meets the three major criteria for an effective laxative as established by physicians*

1. *clinically proven effectiveness*
2. *predictable action*
3. *virtual freedom from griping & other irritating side effects*

*Results of a survey of over 1,000 physicians conducted by the Bureau of Research, Inc., 555 W. Jackson Blvd., Chicago 6, Illinois (April, 1960).

Mead Johnson Laboratories

Symbol of service in medicine

in geriatric patients

PERI-COLACE®

Anthraquinone derivatives from cascara and dioctyl sodium sulfosuccinate, Mead Johnson

eliminates the enema and straining at stool

In geriatric patients,[1,2] Peri-Colace promptly, yet gently, induces bowel movements—satisfactory evacuation without straining. It helps to eliminate the use of enemas for bedfast patients, even where fecal impaction is a complicating factor.[2]

Experience in practice[1,2] has shown the unusual dependability of Peri-Colace in elderly patients with a wide variety of illnesses complicated by constipation. In many of these, muscular strength is insufficient to effect a bowel movement.[2] With Peri-Colace, a soft, easily passed stool is evacuated within 8 to 12 hours.

With Peri-Colace, "...side effects such as griping are reduced to a minimum."[3]

References: (1) Smigel, J. O.; Lowe, K. J.; Hosp, P. H., and Gibson, J. H.: M. Times *86*:1521-1526 (Dec.) 1958. (2) Napp, E. E., and Donnenfeld, A. M.: J. Am. Geriatrics Soc. *8*:858:860 (Nov.) 1960. (3) Broders, A. C., Jr.: Am. J. Digest. Dis. *2*:483-486 (Sept.) 1957.

59161

activities (Continued from page 72A)

either the taxpayer or his wife is 65, medical expenses of both can be deducted.

•

Nephrotic High Blood Pressure

A study of nephrotic high blood pressure is under way at Northwestern University Medical School, sponsored by the National Heart Institute. Nearly 50 physicians will participate in collecting the data that will include records of thousands of patients in the United States and Canada.

•

Our Aging Population

A national crisis is due in about twenty years, according to Dr. Steven M. Horvath of Jefferson Medical College in Philadelphia. By 1980, he said, one-half the population will be over 45 years old and 35 per cent will be over 65. Dr. Horvath has urged all applicable branches of science to head off the aging population crisis by getting together to define the effect of age on the ability to perform work. He said more knowledge is needed about how much physical fitness is required of the aged in order for them to function in society.

•

Appointments

Dr. Blue Carstenson has been appointed assistant to the under secretary, Department of Health, Education and Welfare. He is the former chairman of the technical directors of the White House Conference on Aging and was staff director for senior citizens for Kennedy.

Robert H. Grant, director of the Department of Health, Education and Welfare Special Staff on Aging, has been appointed

(Continued on page 80A)

patients welcome the pleasant way

GUSTALAC

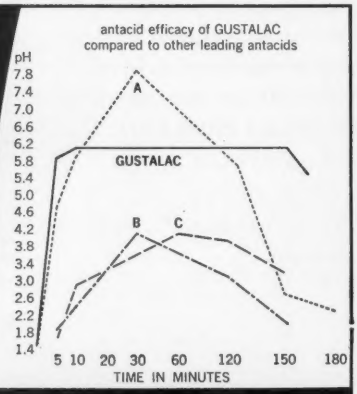
TABLETS

give immediate relief from

Gastric and Duodenal ULCERS

HYPERACIDITY

Heartburn of Pregnancy



Each dose eases pain, "burning" and eructation for 2½ hours — two tablets are equal in buffering value to 10 oz. of milk. Does not cause acid rebound, constipation or systemic alkalosis.

PLEASANT TASTING GUSTALAC tablets each provide: the "most potent antacid,"[1] superfine calcium carbonate (300 mg.), buffer-enhanced by a special high protein defatted milk powder (200 mg.).

DOSAGE: 2 tablets chewed or swallowed q. 2 to 3 h. PRN and on retiring.

1. Kirstner, J. B.: J.A.M.A. 166:1727, 1958.

Samples and literature on request

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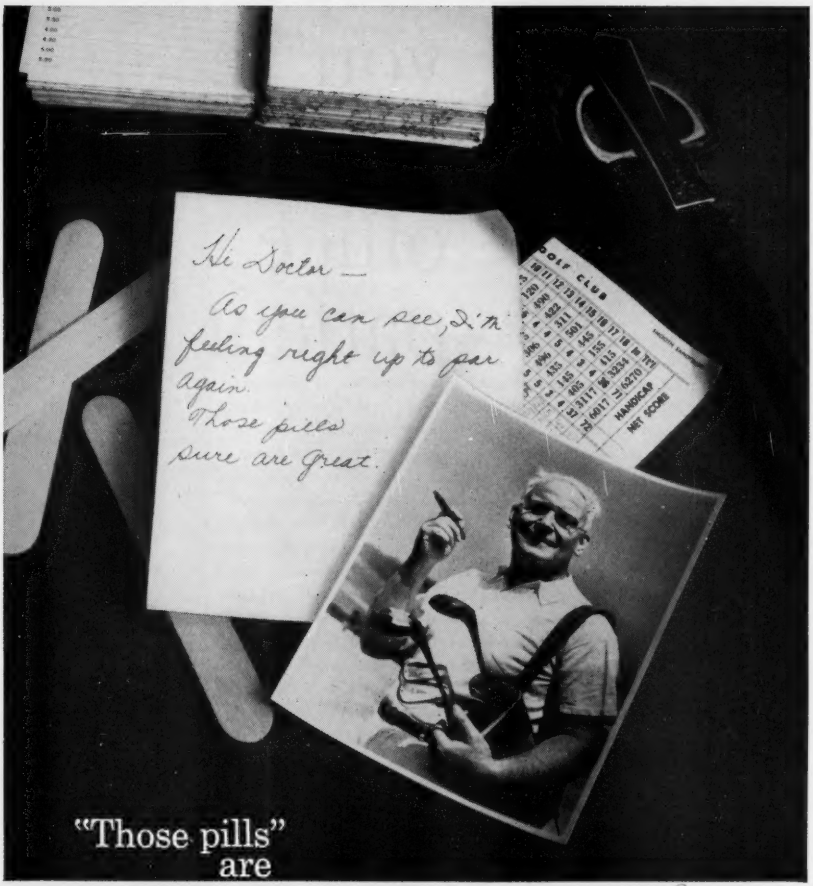

GEVRESTIN®

Geriatric Vitamins—Minerals—Hormones—d-Amphetamine Lederle

one capsule every morning supplements the diet to help achieve proper balance: ❖ nutritionally ❖ metabolically ❖ mentally

Each dry-filled capsule contains: Ethinyl Estradiol, 0.01 mg. • Methyl Testosterone, 2.5 mg. • d-Amphetamine Sulfate, 2.5 mg. • Vitamin A (Acetate), 5,000 U.S.P. Units • Vitamin D, 500 U.S.P. Units • Vitamin B_{12} with AUTRINIC® Intrinsic Factor Concentrate, 1/15 N.F. Oral Unit • Thiamine Mononitrate (B_1), 5 mg. • Riboflavin (B_2), 5 mg. • Niacinamide, 15 mg. • Pyridoxine HCl (B_6), 0.5 mg. • Calcium Pantothenate, 5 mg. • Choline Bitartrate, 25 mg. • Inositol, 25 mg. • Ascorbic Acid (C) as Calcium Ascorbate, 50 mg. • l-Lysine Monohydrochloride, 25 mg. • Vitamin E (Tocopheryl Acid Succinate), 10 Int. Units • Rutin, 12.5 mg. • Ferrous Fumarate (Elemental iron, 10 mg.), 30.4 mg. • Iodine (as KI), 0.1 mg. • Calcium (as $CaHPO_4$), 35 mg. • Phosphorus (as $CaHPO_4$), 27 mg. • Fluorine (as CaF_2), 0.1 mg. • Copper (as CuO), 1 mg. • Potassium (as K_2SO_4), 5 mg. • Manganese (as MnO_2), 1 mg. • Zinc (as ZnO), 0.5 mg. • Magnesium (MgO), 1 mg. *Supply:* Bottles of 100 and 1,000.

Request complete information on indications, dosage, precautions and contraindications from your Lederle representative or write to Medical Advisory Department.

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helps
you "reach"
the depressed
office
patient

NIAMID®

BRAND OF NIALAMIDE

provides remission of depression—smoothly, gradually, without "jarring" □ notably low incidence of serious complications or side effects □ convenience of once-a-day dosage

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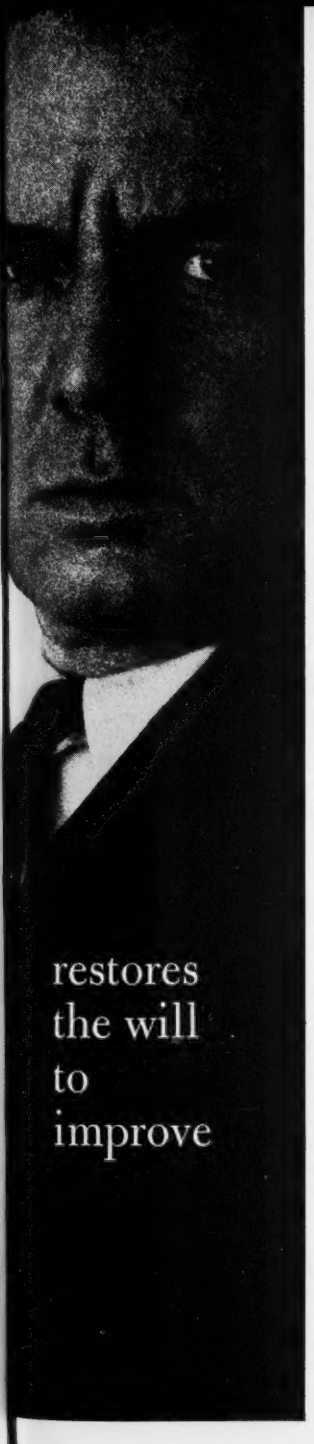

restores
the will
to
improve

In Brief Niamid, brand of nialamide, is 1-(2-[benzylcarbamyl] ethyl)-2-isonicotinyl-hydrazine, a well-tolerated antidepressant that may correct or relieve depression on once-a-day dosage. **Indications:** Depressive syndromes of varying degrees of severity may be responsive to Niamid including: involutional melancholia, postpartum depression, depressed phase of manic-depressive reaction, senile depression, reactive depression, schizophrenic reaction with depressive component, psychoneurotic depression. ■ In neurotic or psychotic patients, Niamid may normalize or favorably modify aberrant or excessive reactions and symptoms of depression such as: phobias, guilt feelings, dejection, feeling of inadequacy, discouragement, worry, uneasiness, distrustfulness, hypochondriacal and nihilistic ideas, difficulty in concentration, insomnia, loss of energy or drive, indecision, hopelessness, helplessness, decreased functional activity, emotional and physical fatigue, irritableness, inability to rest or relax, sadness, anorexia and weight loss, and withdrawal from society. *In the withdrawn patient,* Niamid may elevate the mood so that there is increased activity, increased awareness and interest in surroundings, and increased participation in group activities. Appetite may be increased and there may be decreased fatigability. Lack of clinical response to other antidepressant therapy does not preclude a favorable response to Niamid. Relief of depression may also be evidenced by elimination or reduction of the need for somatic therapy, such as electroshock. *In patients suffering from depression associated with chronic illness,* Niamid may improve mental outlook, reduce the impact of pain, decrease the amounts of narcotics or analgesics needed, and improve appetite and well-being. *In patients with angina pectoris,* Niamid has been found to be a useful adjunct to management through reduction in frequency of attacks and pain. **Dosage:** Starting dosage is 75 to 100 mg. on a once-a-day or divided daily basis. This may subsequently be adjusted depending upon the tolerance and response. Responses to Niamid are not usually rapid, and revisions of dose should be withheld until at least a few days have elapsed at each level. Increments or decrements of 12½-25 mg. are generally sufficient. A daily dosage of 200 mg. is the maximum recommended for routine use. (As much as 450 mg. daily has been used in some patients.) **Side Effects:** Niamid, in clinical use, has been characterized by a significant lack of toxicity. It is generally well tolerated. Nervousness, restlessness, insomnia, hypomania, or mania, sometimes occur. Occasional headache, weakness, lethargy, vertigo, dryness of the mouth, blurred vision, increased perspiration, constipation, mild skin rash, mild leukopenia, and epigastric distress may be obviated or modified by reductions in dose. Effects due to monoamine oxidase inhibition persist for a substantial period following discontinuation of the drug. **Precautions and Contraindications:** Hepatic toxicity has not been reported in extensive clinical studies. However, if previous or concurrent liver disease is suspected, the possibility of hepatic reactions and liver function studies should be considered. ■ The suicidal patient is always in danger, and great care must be exercised to maintain all security precautions. The apathetic patient may obtain sufficient energy to harm himself before his depression has been fully alleviated. ■ Niamid may potentiate sedatives, narcotics, hypnotics, analgesics, muscle relaxants, sympathomimetic agents, thiazide compounds and stimulants, including alcohol. Caution should be exercised when rauwolfia compounds and Niamid are administered simultaneously. Rare instances have been reported of reactions (including atropine-like effects, and muscular rigidity) occurring when imipramine was administered during or shortly after treatment with certain other drugs that inhibit monoamine oxidase. **In Cardiology:** The central effects of Niamid may encourage hyperactivity and the patient should be closely observed for any such manifestation. Orthostatic hypotension or hypertensive episodes occur in a few individuals; cardiac patients should be carefully selected and closely supervised. **In Epilepsy:** Although in some patients therapeutic benefits have been achieved with Niamid, in others the disease has been aggravated. Care should be exercised in the concomitant use of imipramine, since such treatment with monoamine oxidase inhibitors has been reported to aggravate the grand mal seizures. **In Tuberculosis:** Existing data do not indicate whether resistance of M. tuberculosis to isoniazid may be induced with Niamid therapy; nevertheless, it should be withheld in the depressed patient with coexisting tuberculosis who may need isoniazid. ■ As with all therapeutic agents excreted in part via the kidney, due caution in adjusting dosage in patients with impaired renal function should be observed. **Supplied:** Niamid (Nialamide) Tablets, 25 mg.: 100's—pink, scored tablets; 100 mg.: 100's—orange, scored tablets./*More detailed professional information available on request.*

IN CHRONIC URINARY TRACT INFECTIONS

UROLITIA

Soothes... Burning Urination

CLEARS... Infected Urine

Urolitia is bacteriostatic, bactericidal, non-toxic, does not produce drug-fastness, provides simple dosage, and is economical for long term therapy.

Urolitia rapidly controls E. coli, S. albus, and S. aureus infection. Its soothing action is due to the prompt release of Triticum and Zea extractives by the kidney into the inflamed bladder.

Samples on Request

Urolitia is especially useful for elderly patients with residual urine due to cystocele or enlarged prostate, in whom permanent sterilization of the urine cannot be expected.

CONTAINS NO DYES

Urolitia—each tablespoonful contains:

Methenamine	20 gr.
Lithium Benzoate	5 gr.
Sodium Benzoate	2 gr.

In a soothing, demulcent menstruum of Triticum and Zea.

Dose: 1 Tbs. in ½ cup warm water ½ hr. a.c. and h.s. Decrease dose after second day.

Supplied: Bottles of 8 fl. oz.

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$1,000 to $5,000

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A nationwide Executive Loan Service designed for responsible professional men as a convenient supplementary source of personal credit. No collateral, no endorsement, no embarrassing investigation. All details handled by mail from the privacy of your office. Monthly repayments up to 2 years if desired. References:

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Industrial Credit Company

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activities (Continued from page 76A)

assistant chief of the Office of International Research of the National Institutes of Health.

Mrs. Mary Cleverley, specialist in housing for the elderly, has been appointed assistant commissioner on housing for the elderly with the U. S. Public Housing Administration. Local citizen, civic, business, and professional groups that are interested in having Mrs. Cleverley explain the programs for housing aged persons with low incomes may contact her at Longfellow Building, Washington 25, D. C.

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Senate Aging Committee

The Senate Special Committee on Aging has been expanded from 9 to 21 members. New members are: Democrats—Wayne Morse (Oregon), Alan Bible (Nevada), Joseph S. Clark (Pennsylvania), Frank Church (Idaho), A. Smith (Massachusetts); and Republicans—Frank Carlson (Kansas), Wallace F. Bennett (Utah), Prescott Bush (Connecticut), and Kenneth B. Keating (New York).

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Training Course for Nursing Home Administrators

The California State Department of Public Health has contracted with the Attending Staff Association of the Rancho Los Amigos Hospital in Los Angeles to develop a $50,000 training project for owners and administrators of nursing homes, sanitariums, rest homes, and homes for the aged. The course is supported by funds from the USPHS 1961 General Health Grant and is under the direction of Drs. John Gerletti and C. C. Crawford, both of the University of Southern California.

The program will include information in fields such as medicine, rehabilitation, nursing, mental hygiene, geriatrics, and public health, as well as in hospital administration and business management. For more information write Drs. Gerletti and Crawford at Rancho Los Amigos Hospital, 7601 East Imperial Highway, Downey, California.

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brand of bisacodyl tablets and suppositories

the laxative with a bibliography

Geigy

The extensive bibliography* on Dulcolax, amounting to almost 100 clinical reports, strongly affirms its clinical advantages.

Induces Natural Evacuation
The action of Dulcolax is based on simple reflex production of large bowel peristalsis on contact with the colonic mucosa. As a result, stools are usually soft and well formed and purgation is avoided.

Predictable Action
With Dulcolax tablets action is almost invariably obtained overnight... with suppositories action occurs within the hour.

Wide Application
Dulcolax is as well adapted to preparation for radiographic and operative procedures as it is to the treatment of constipation.

*Detailed literature, including complete bibliography, available on request.

Dulcolax®, brand of bisacodyl: Tablets of 5 mg. and suppositories of 10 mg. Under license from C. H. Boehringer Sohn, Ingelheim.

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Division of Geigy Chemical Corporation
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YOUR UNRESPONSIVE "ARTHRITIC" MAY BE SUFFERING FROM CHRONIC GOUTY ARTHRITIS

At least 5 per cent of all patients suffering from arthritis really have gouty arthritis.[1] Although frequently overlooked,[2] gouty arthritis is readily diagnosed if one remembers this possibility in all patients with chronic joint distress. Elevated serum uric acid levels, pain relief with colchicine and occurrence of tophi are valuable diagnostic aids. Once clinically confirmed, chronic gouty arthritis responds successfully to TRIURATE.®

TRIURATE combines in **one** tablet three effective agents for the management of gouty arthritis: FLEXIN® Zoxazolamine,* a potent uricosuric agent; Colchicine, for preventing acute attacks; and TYLENOL® Acetaminophen, the effective analgesic which does not interfere with uricosuric action. Thus, TRIURATE promptly relieves chronic discomfort, prevents acute flare-ups, reduces tophi, and prevents formation of new deposits.

TRIURATE

the full-range therapy for gouty arthritis and chronic gout

Average Dose: One tablet three times a day after meals. **Supplied:** Beige, scored tablets, imprinted McNEIL, bottles of 50. Each tablet contains: FLEXIN® Zoxazolamine® 100 mg., Colchicine 0.5 mg., and TYLENOL® Acetaminophen 300 mg.

(1) Boland, E. W.: World-Wide Abstr. Gen. Med. 3:11, 1960. (2) Lockie, L. M.: Am. J. Orthopedics 2:252, 1960.

*U.S. Patent No. 2,890,985

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Take an "inside look" at a remarkable advance in topical steroid therapy

The unique base, Veriderm, combined with the outstanding anti-inflammatory steroid, Medrol, provides effective treatment of dermatoses.

Veriderm Medrol Acetate consists of Veriderm, a base closely approximating the composition of normal skin lipids, and Medrol Acetate, the highly effective, dependable corticoid.

Topical use of Veriderm Medrol Acetate produces symptomatic relief and objective improvement of dermatoses, and at the same time aids in correcting dry skin conditions. Veriderm Medrol Acetate, less greasy than an ointment and less drying than a lotion, is indicated in atopic, contact, or seborrheic dermatitis, and in neurodermatitis, anogenital pruritus, and allergic dermatoses.

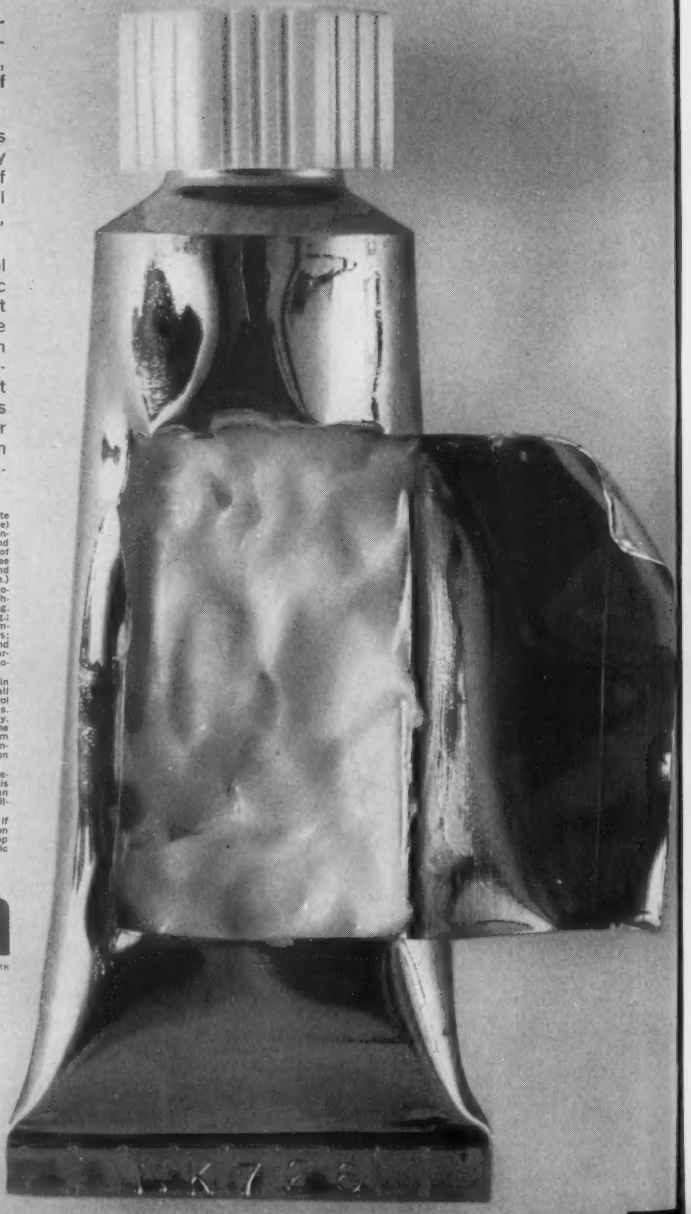
Available in four formulations: Veriderm Medrol Acetate 0.25% — Each gram contains: Medrol (methylprednisolone) Acetate 2.5 mg.; Methylparaben 4 mg.; Butyl-p-hydroxybenzoate 3 mg.; in a skin lipid base composed of saturated and unsaturated free fatty acids; triglycerol and other esters of fatty acids; saturated and unsaturated hydrocarbons; free cholesterol; high-molecular-weight alcohol; with water and aromatics. (Veriderm Medrol Acetate 1% is also available.)
For prophylaxis against secondary infection: Veriderm Neo-Medrol Acetate 0.25% — Each gram contains: Medrol (methylprednisolone) Acetate 2.5 mg.; Neomycin Sulfate 5 mg. (equivalent to 3.5 mg. neomycin base); Methylparaben 4 mg.; Butyl-p-hydroxybenzoate 3 mg.; in a skin lipid base composed of saturated and unsaturated free fatty acids; triglycerol and other esters of fatty acids; saturated and unsaturated hydrocarbons; free cholesterol; high-molecular-weight alcohol; with water and aromatics. (Veriderm Neo-Medrol Acetate 1% is also available.)
Administration: After careful cleansing of the affected skin to minimize the possibility of introducing infection, a small amount of either Veriderm Medrol Acetate or Neo-Medrol Acetate is applied and rubbed gently into the involved areas. Application should be made initially one to three times daily. Once control is achieved — usually within a few hours — the frequency of application should be reduced to the minimum necessary to avoid relapses. The 1% preparation is recommended for beginning treatment and the 0.25% preparation for maintenance therapy.
Contraindications: Local application of Veriderm Medrol Acetate or Neo-Medrol Acetate is contraindicated in tuberculosis of the skin and in other cutaneous infections for which an effective antibiotic or chemotherapeutic agent is not available for simultaneous application.
These preparations are usually well tolerated. However, if signs of irritation or sensitivity should develop, application should be discontinued. If bacterial infection should develop during the course of therapy, appropriate local or systemic antibiotic therapy should be instituted.
Supplied in 5 Gm. and 20 Gm. tubes.

Veriderm

TRADEMARK

Medrol† Acetate

Neo-Medrol† Acetate



†TRADEMARK, REG. U. S. PAT. OFF.

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How to help your patient stick to a high protein diet

The secret ingredient in a successful diet is acceptance. And a diet that offers as many and such appetizing foods as this is sure to win the approval of your patient! A fluffy omelette filled with frankfurter slices is a delicious source of protein, as are ground meat and flaked fish. Cottage cheese makes a flavorful side dish or satisfying filling for dark bread sandwiches. Hot weather suppers call for mixed green salad topped with meat and cheese slices... followed by chilled fruit.

A glass of beer can add zest to a patient's diet.

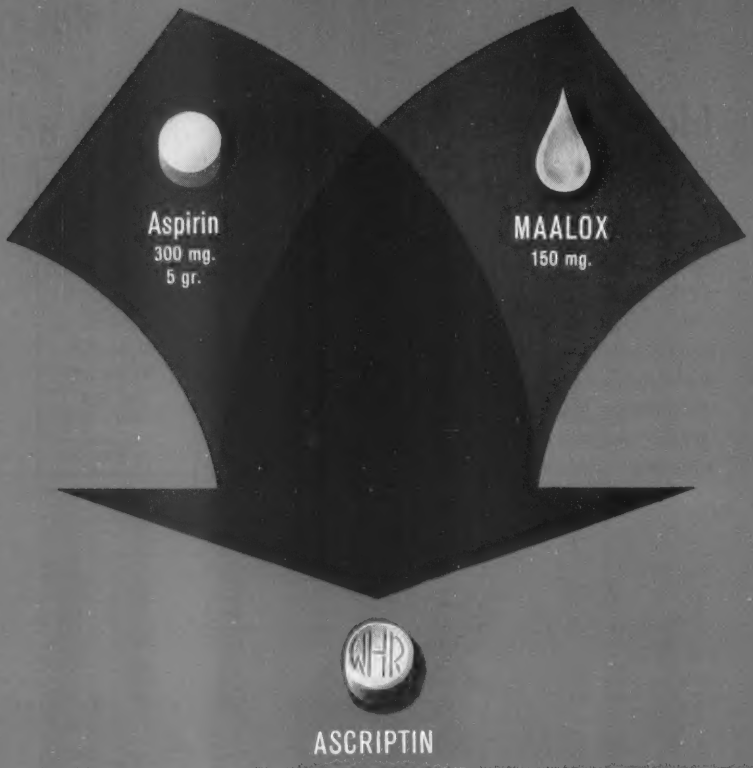
Protein 0.8 Gm;
Calories 104/8 oz. glass
(Average of American Beers)

Diet patients welcome varied fare like this.

United States Brewers Association, Inc.

For reprints of this and 11 other diet menus, write us at 535 Fifth Avenue, N. Y. 17, N. Y.

aspirin buffered with the most widely-prescribed antacid...



in long-term administration, as in Arthritis, when aspirin combined with an antacid is desired:

Specify **Ascriptin**® RORER

the aspirin buffered with the best

To prevent or minimize gastric distress which often accompanies prolonged or high level administration of acetylsalicylic acid, ASCRIPTIN provides aspirin in combination with MAALOX®, the preferred professional antacid. The recognized superiority of MAALOX makes ASCRIPTIN a superior aspirin-antacid, with the virtues of buffered aspirin and with the added distinction of being promoted professionally only.

Indicated wherever salicylates are useful, ASCRIPTIN is particularly suited to the long-term requirements of your arthritic patients.

Supplied: Bottles of 100 and 500 tablets. For severe pain — Capsules ASCRIPTIN with Codeine (codeine phosphate 15 mg.), bottles of 50.

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Now arthritic flare-ups can be controlled with much lower steroid dosages

With Somacort to relax muscles and relieve pain, tender joints need far less steroid to reduce inflammation

Somacort is a safe, logical step-up in treatment during the rough days when your patients need more than salicylates to keep comfortable and active.

Soma, by itself, benefits many arthritics by relieving the muscle spasm and pain which arise from joint inflammation. Thus with Somacort, which combines Soma with prednisolone, the amount of steroid needed to control inflammation[1] can be kept within more conservative limits.

Somacort is well tolerated even when used for long-term therapy in more serious cases.

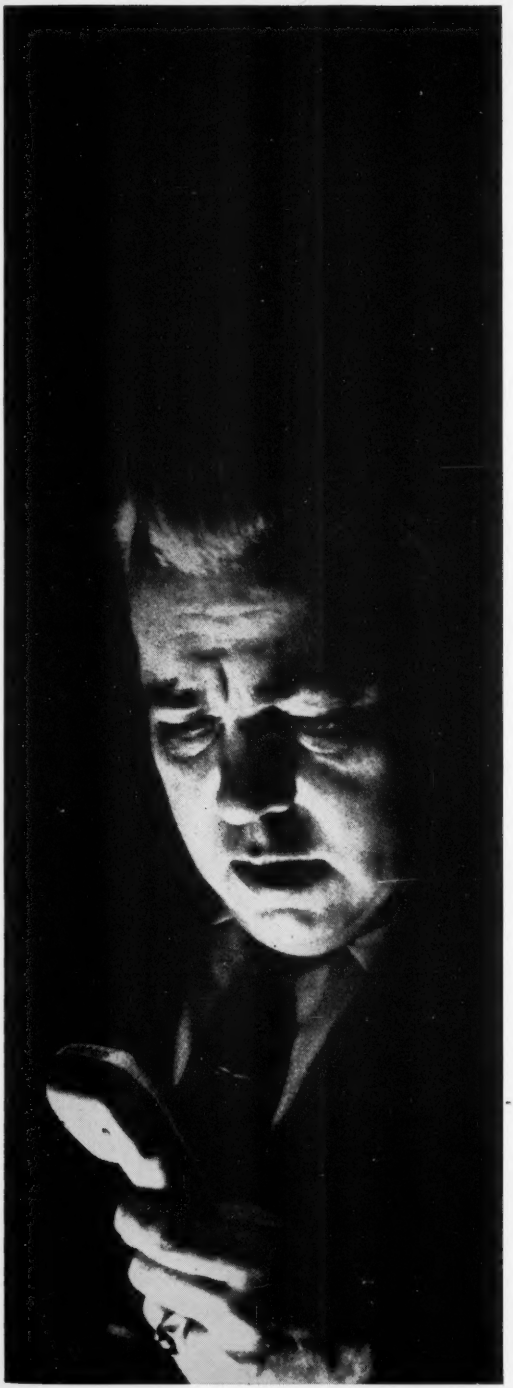
1. Wein, A.B.; The Use of Carisoprodol (SOMA) in Orthopedic Surgery and Rehabilitation, Miller, James G., ed., Wayne State University Press, Detroit, Michigan, 1959.

Recommended dosage: 1 or 2 tablets q.i.d. (Each tablet contains 350 mg. carisoprodol, 2 mg. prednisolone)

SOMACORT™

(carisoprodol, Wallace, with prednisolone)

Wallace Laboratories, Cranbury, New Jersey



Day and night–

less wheezing, coughing, labored respiration in chronic bronchitis and emphysema

New Isuprel Compound Elixir is a balanced expectorant bronchodilator. It contains potassium iodide to promote expectoration and relieve dry cough. Its three bronchodilators, Isuprel, ephedrine, and theophylline, keep bronchi continuously dilated. Luminal is included to negate possible side effect from adrenergic medication and to provide very mild sedation for the patient.

New Isuprel Compound Elixir alleviates symptoms...prolongs relief in chronic bronchitis and emphysema.

Each good-tasting vanilla-flavored tablespoon (15 cc.) contains:

Isuprel® (brand of isoproterenol) HCl	2.5 mg.
Ephedrine sulfate	12 mg.
Theophylline	45 mg.
Potassium iodide	150 mg.
Luminal® (brand of phenobarbital)	6 mg.
Alcohol	19%

Adult Dose: 2 tablespoons 3 or 4 times daily.

How Supplied: Isuprel Compound Elixir is supplied in bottles of 16 fl. oz.

New ISUPREL® compound ELIXIR

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New York 18, N.Y.

ISUPREL AND LUMINAL, TRADEMARKS REG. U. S. PAT. OFF.

NEW PRODUCT

End the Spin and Spell of "Dizziness"

vertigo and nausea

associated with:

cerebral ischemia

labyrinthine dysfunction

Meniere's syndrome

● **TIGACOL PREVENTS DIZZINESS WITHOUT CAUSING DROWSINESS** through two specific-acting agents: Roniacol controls vertigo promptly by direct relaxation of peripheral blood vessels and its effects last twice as long as nicotinic acid; Tigan controls the nausea, so often associated with vertigo, by selective suppression of emetic impulses . . . without causing drowsiness, adrenergic effects or significant hypotension.

USUAL ADULT DOSAGE: One or two capsules three times daily.

Roniacol®—brand of nicotinyl alcohol. Tigan®—4-(2-dimethlyaminoethoxy)-N-(3,4,5-trimethoxybenzoyl) benzylamine

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